**Name of journal: World Journal of Ophthalmology**

**ESPS Manuscript NO: 5193**

**Columns: MINIREVIEWS**

Melatonin and derivatives as promising tools for glaucoma treatment

Alkozi HA *et al.* Melatonin and analogues reduce IOP

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**Supported by** Universidad Complutense de Madrid, No. GR35/10-A-920777; the Ministry of Economy, No. SAF 2010/16024; the Institute Carlos III, No. RETICS RD12/0034/0003

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**Received:** August 21, 2013 **Revised:** November 5, 2013

**Accepted:** November 12, 2013

**Published online:**

**Abstract**

Neuro-hormone Melatonin and its analogues are presenting an important physiological and pharmacological ability to reduce intraocular pressure (IOP), thus, they are suitable for the treatment of ocular hypertension often associated to glaucoma. It is demonstrated that two of its analogues, 5-MCA-NAT and IIK7, are more effective than melatonin to reduce IOP for 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 resemblance to melatonin structure, are being tested as potential glaucoma drugs. In this sense, agomelatine which is already used as anti-depressant medicine is recognized as 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 it should be taken under serious consideration.

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**Key words:** 5-MCA-NAT; IIK7; Glaucoma; Ocular hypertension; Melatonin.

**Core tip:** This minireview depicts the main features of melatonin and derivatives as interesting agents for the treatment of the ocular hypertension associated to glaucoma.

Alkozi HA, Pintor J. Melatonin and derivatives as promising tools for glaucoma treatment.

**Available from:**

**DOI:**

**INTRODUCTION**

There is a general interest on searching of novel compounds, capable to reduce intraocular pressure (IOP), as an improved alternative to the existing drugs. Lowering IOP can be reached through the reduction of aqueous humour production or by increasing its outflow through trabecular meshwork or uveoscleral pathways. The interest for searching new compounds relies on the fact that most of the existing drugs produce important side effects, hampering the treatment on certain patients. Side effects are common issue on glaucoma medications. β-blockers such as timolol can cause bradycardia and hypotension and they are unsuitable for patients suffering from cardio vascular problems [[1](#_ENREF_1)], asthma, obstructive pulmonary disease or corneal dystrophy [[2](#_ENREF_2)]. Cholinergic agonists such as pilocarpine, produce fixed pupils and induce myopia and cataracts [[1](#_ENREF_1)], whereas prostaglandins (*e.g.*, Latanoprost) cause eyelash growth, 999iris pigmentation[[3](#_ENREF_3)] and muscle and joint pain [[2](#_ENREF_2)]. Frequently, ocular redness and ocular surface discomfort obligates patients to abandon the treatments.

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](#_ENREF_4)]. Among these, the neuro-hormone melatonin emerges as a promising substance with interesting hypotensive properties [[5](#_ENREF_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 and is not causing redness or corneal oedema. In general ocular examinations, it was not noticed negative effect [[5](#_ENREF_5)]. It is important to bear in mind that most of melatonin intake is not performed by prescription, as considered a dietetic supplement. In this case high dosages and an elevated number of intakes could produce some minor side effects. Mayo Clinic indicates that the most common side effects are drowsiness, headache and dizziness. Moreover, important doses of melatonin can interfere on some medications such as anticoagulants, immunosuppressants, diabetes medications and birth control pills.

There are two interesting works describing the melatonin effect and of its analogues on reducing IOP. Serle *et al*[[6](#_ENREF_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 substantially IOP, which is recommendable during phacoemulsification [[7](#_ENREF_7)].

From these two relevant works is arising the question 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 pineal gland where it is synthesised in low illumination conditions, like it is happening during the night[[8](#_ENREF_8)] and it regulates many day-night processes, called circadian[[9](#_ENREF_9)]. It is necessary to emphasize that this substance is also synthesised in other tissues and ocular structures such as the retina, the ciliary body or the lens. This is clearly suggesting that melatonin can exert some local actions on the tissues where it is synthesised or in surrounding areas. Having in mind that melatonin is released by the lens or the ciliary body it comes to speculate about its presence in the aqueous humour, modifying the physiology of these structures being bathed in the fluid. 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). Considering the circadian pattern of melatonin production it is possible that both processes are associated. 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](#_ENREF_10)]. This effect is similar to that endogenous melatonin does at night reducing IOP. Despite the acquired hypotensive effect, the rapid return to normal pressure values is suggesting that either is necessary to regulate the doses or to look for an alternative compound to produce more sustained effect [[11](#_ENREF_11)].

There are several commercially available melatonin analogues depicting similar behaviour to melatonin. Two compounds are presenting sharper and longer-lasting effects on reducing the IOP compared to melatonin. In particular the compound N-butanoyl-2-2-methoxy-6H-isoindolo(2,1-a]indol-11-yl)ethanamine (abbreviated as IIK7) in which the hypotensive effect lasts up to 7 h, 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](#_ENREF_12)]. Consequently, 5-MCA-NAT is more interesting since it presents longer-term effect depicting a significant reduction of IOP for up to 96 h. This remarkable effect was taken well into consideration as we indicate below [[11](#_ENREF_11)] (Table 1).

5-MCA-NAT was tested in normotensive models but also 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 days reduced IOP from 1 h 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](#_ENREF_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%). There were not observed adverse ocular or systemic side effects during the 5 treatment days, suggesting that this compound could be used perfectly as ocular hypertension treatment [[6](#_ENREF_6)] (Table 1).

Concerning IIK7, it reduced intraocular pressure by acting through MT2 melatonin receptors presumably decreasing aqueous humour formation. Its effect is concentration dependent and it can reduce IOP 38.5 ± 3.2% when compared to control (Table 1). It is important to notice that these experiments were not performed yet in glaucomatous monkeys but only in rabbits [[12](#_ENREF_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 better understood are the protein membrane receptors and until recently there have been cloned three proteins. Two of these membrane receptors termed MT1 and MT2, are melatonin receptors belonging to the 7-transmembrane G protein-coupled receptor family (GPCR). A third receptor has been claimed to exist, 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](#_ENREF_9)]).

MT1, MT2 and the probable MT3 melatonin receptors are present in several ocular structures, according to pharmacological, biochemical and immunological studies [[13](#_ENREF_13),[14](#_ENREF_14)]. This evidence is suggesting that melatonin plays a role in ocular tissues physiological processes, 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, are producing a dissimilar IOP reduction, depending on the compound under study. The use of selective antagonists for melatonin receptors has permitted to identify the presence of MT2 melatonin receptors in the ciliary body of experimental animals such as New Zealand white rabbits. This has been confirmed through immunohystochemical studies. In these studies it has been possible to verify the MT2 melatonin receptors presence on pigmented and non-pigmented ciliary epithelia. Accordingly, the application of melatonin, or IIK7, which is a selective MT2 agonist, is producing a reduction in the production of the aqueous humour [[12](#_ENREF_12)].

5-MCA-NAT has been suggested as an MT3 melatonin receptor agonist reducing IOP. Till date it is unknown the location of the receptor. As there is a controversy with the possible identification of MT3 receptor which is tentatively identified in some animal models as QR2, there were performed some sophisticated experiments to clarify the issue [[15-17](#_ENREF_15)]. In New Zealand rabbits, the use of a siRNA silencing QR2, (therefore avoiding the expression of this enzyme) did not abolished the hypotensive effect of 5-MCA-NAT, clearly indicating that in this animal model MT3 ≠ QR2, opening the possibility to speculate the existence of a receptor that needs to be cloned to fully understand its functioning and location [[18](#_ENREF_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 humour.

Till date, it has been possible to demonstrate that 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 get 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 inhibitors action, such as dorzolaminde or azetazolamide [[19](#_ENREF_19)].

Likewise, by the application 5-MCA-NAT is modified the expression of adrenergic receptors. Interestingly, this melatonin analogue is able to produce a sequential process consisting of an initial reduction in the β2-adrenoreceptors expression, followed by an increase in α2A-adrenoreceptors[[20](#_ENREF_20)]. Altogether these consecutive effects produce a sustained reduction in IOP lasting for at least 9 6h [[21](#_ENREF_21)].

In summary, 5-MCA-NAT apart from a sharp hypotensive effect, it exerts a long term-effect, maintaining the IOP low 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](#_ENREF_5)]. Inspire Pharmaceuticals Inc. (Now absorbed by Merck), has designed several melatonin analogues with interesting hypotensive properties in reducing IOP. In recent studies melatonin analogues termed INS48848, INS48852 and INS48862 demonstrated similar behaviour as melatonin, 5-MCA-NAT, and IIK7[[22](#_ENREF_22)]. Indeed, these three compounds decreased IOP in a dose-dependent manner similar to melatonin, 5-MCA-NAT, and IIK7, confirming their efficiency on 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 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 on reducing IOP and especially when it is abnormally elevated [[22](#_ENREF_22)].

Another alternative to the development of newly synthesised compounds is to search for melatoninergic compounds already used for other medical purposes. Compounds such as Ramelteon ((S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide)), also known as *Rozerem*, used for sleep disorders[[23](#_ENREF_23)] or Agomelatine (N-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide), known also by the names *Valdoxan, Melitor, Thymanax* [[24](#_ENREF_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 is topically applied on rabbit eyes. Agomelatine (10 μL, 100 μmol/L) reduced IOP by 20.8% ± 1.4% and its maximal IOP reduction was 180 min 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% ± 5.7% (Figure 3, Table 1) [[25](#_ENREF_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 be performed an exhaustive study on the role of melatonin and its analogues in the different ocular structures, since it is very probable this knowledge to contribute in the discovery of more effective treatments for pathologies like glaucoma, corneal wound healing, cataracts or retinal pathology[[26](#_ENREF_26)].

Taking into account the importance of the role of melatonin and its analogues in hypertension, often associated to 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, even though further research is required to prove that they can be safely used as treatment for the 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 melatoninergic compounds. For instance, melatonin itself is able to reduce IOP in normotensive humans as previously described[7]. These authors report an approximate 30% of 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 in hypertensive animals, being more effective in hypertensive than in normotensive animals (Table 1). Also, experiments performed with 5-MCA-NAT on hypertensive monkeys, a previous step before human clinical trials, have proved that this melatonin analogue was reducing IOP.

As a 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 depression treatment drug under the commercial name Valdoxan[24]. Since many of the pre-clinical tests have been already completed, we should not be surprised if agomelatine starts clinical trials, becoming the first melatoninergic compound joining the group of glaucoma treatment substances.

**ACKNOWLEDGEMENTS**

HAA is a fellowship holder of Saudi Arabia Government.

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**P-Reviewers:** Clement CI, Hong YJ, Nowak MS, Zanon-Moreno V **S-Editor:** Song XX **L-Editor: E-Editor:**

**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).

**Figure 2 Expression of mRNA levels in ciliary body cells.** The amounts of mRNA and concomitantly adrenoceptors were changed after the application of 5-MCA-NAT. While there was an increase of α2A-adrenoreceptors (in red), there was a decrease in the levels of β2-adrenoreceptors.

**Figure 3** **Comparative effects of melatonin and analogues in an animal model.** Equal doses of melatonin or the corresponding analogues (100 μmol/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).

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound**  **species** | **IOP reduction** | **Receptor**  **involved** | **Ref.** |
| Melatonin  Human  Rabbit  Mouse (glaucomatous) | 32.01%±3.25%  22.0% ± 1.6%  33.4% ± 2.5% | Unknown  MT2, MT3  MT2 | [7]  [10, 11]  UD |
| 5-MCA-NAT  Monkey (hypertensive)  Rabbit | 19.2% ± 2.1%  42.5% ± 1.6% | MT3  MT3 | [6]  [10, 11] |
| IIK7  Rabbit | 38.5% ± 3.2% | MT2 | [12] |
| INS48848  Rabbit | 36.0% ± 2.0% | MT3 | [22] |
| INS48852  Rabbit | 33.1% ± 1.4% | MT2 | [22] |
| INS48862  Rabbit | 26.0 ± 1.3 V | MT2 | [22] |
| Agomelatine  Rabbit  Normotensive  Hypertensive | 20.8% ± 1.4%  68.8% ± 5.7% | MT2  MT2 | [25]  [25] |

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