ANSWERS TO THE REFEREES

We wish to thank all the referees for their kind comments and suggestions regarding our manuscript. For sure all these comments will improve the final version of this manuscript. The changes and amendments have been done in red colour in order to make them easy to find.

Answers to referee 1

1. Please revise this manuscript with English native speakers because it has so many grammatically incorrect expressions. It was hard to read and understand sometimes.

The referee is right. We have done an exhaustive revision of the grammar and style.

2. In this manuscript, many melatonin analogues are listed as an alternative IOP-lowering agents. However, any agents are not supported by animal or human-based study concerning how much IOP can be lowered, except agomelatine. Please add the data from the animal-study or in vitro study.

We understand is that the referee wants the data of the IOP reduction for the different melatoninergic compounds in the different models. In this sense, we have included a table in which the animal models, IOP reduction, conditions (normotensive or hypertensive, when available) and the receptors involved in the hypotensive action, are described.

3. Please mention about the limitation or adverse effects of melatonin treatment.

We have added a paragraph describing the limited number of side effects of melatoninergic compounds. At the end of page 3 we have added the following text:

"…With no known side effects when applying to the eye, it has been observed that using 5-MCA-NAT (a melatonin analogue, see below) does not produce redness, corneal oedema; it does not affect the corneal and lens transparency. In a general ocular examination, there was no negative effect [5]. It is important to bear in mind that most of melatonin intake is not by prescription but as a dietetic supplement. In this case the dosages and the number of intakes can change and some side effects might appear. Mayo Clinic indicates that the most common side effects are daytime sleepiness, headache and dizziness. Moreover, important doses of melatonin can interfere some medications such as anticoagulants, immunosuppressants, diabetes medications and birth control pills."

Answers to referee 2

1.- I have a major concern, which is the use of English and grammar. The manuscript should be revised by the native speaker because there is a lot of language errors, what sometimes makes it difficult to understand.

We totally agree with the referee and this point has been revised.

2.- Also in my opinion the authors should shorten these two chapters about receptors into one. In the introduction section you have written that topical beta-blockers may cause systemic hypertension, which is a mistake. Their side-effect is rather systemic hypotension, so please change it.

We have merged the parts on "melatonin receptors" and "long term effects" into a single one.

We have also corrected the indicated mistake in the introduction.

Answers to referee 3

1.- Please have the manuscript reviewed for English grammar and spelling.

We have revised English grammar and spelling as suggested.

2. Discussion of the potential adverse effects or problems relating to melatonin treatment should be included.

We have added a paragraph describing the limited number of side effects of melatoninergic compounds. At the end of page 3 we have added the following text:

*"…*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]. 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…"

3. A focussed discussion on evidence in humans should be included as most of the data presented in this review is from animal studies.

The referee is right, so we have added a paragraph on this regard at the end of the manuscript, page 11:

"...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 (see 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…"

Answers to referee 4

1.- The only point that I do not like is the section of references. There are a total of 26 citations, of which 13 (50%) are previous works of the authors of this manuscript. In my opinion, it is an exaggerated number of self-citations.

The referee is right, approximately 50 % of the references are self references. A quick search in the pubmed with the words "melatonin" and "IOP", provides 44 record (the oldest from 1984). From those, we have published 15.

A careful observation demonstrates that all of the quoted references, ours and those from other groups, are necessary. We thought it would be interesting to indicate our main contribution to the field, and therefore the presence of each of the references has been clearly justified by the written text.