OPEN PEER REVIEW

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Peer Review Report for "Alteration of Hematologic Parameters in Morphine-Dependent Rats by Long-Term Administration of Orexin Type 1 Receptor Antagonist"

Author(s): Zahra Piri, Masoumeh Kourosh Arami, Minoo Shahidi, Somayeh Nazari

Review Timeline:

- Submit Date: 26 Oct 2019
- Revised Date: 14 Apr 2020
- Accepted Date: 15 Apr 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

4 Dec 2019

Dear AE,
In this manuscript, the authors found that orexin-A receptor antagonist SB-334867 could reduce several hematologic factors in morphine-depended rats, such as white blood cell count, platelet cell count, and hematocrit. Several concerns are listed below.
1. In this manuscript, the authors set up 4 experimental groups, control, morphine alone, SB-334867, and SB-334867 with morphine. It would be better to add one more group in the experimental setup, treat the rats with morphine first, then add the receptor antagonist SB-334867. This will be more related to human study, people usually use morphine first, then you need to treat them. Please make sure all the Ns in each group are correct. For example, the control group, they has 6 mice, but in the method part, the authors said 7 per group.
2. The authors mentioned in the DATA ANALYSIS part, morphine withdrawal symptoms, How did increased/ reduced MCHC, WBC, and platelet cells count related to morphine-withdrawal symptoms?
3. How does this research apply to clinical study?
4. Please go through the manuscript and correct misspellings.

Thanks

REFEREE: Reviewer | **Revision** (0) 1 Jan 2020

Dear AE,
I read the manuscript carefully and I think the subject has enough appeal to print in the journal but it has some structural and other problems that you must answer to them.
• The basic problem is about the study design that the authors did not have a sham group; Since At first, they should demonstrate statistically that there was no significant difference between the sham and vehicle groups and then compared other groups with these. So if they could correct this problem, their work will be defensible and judgmental, otherwise it will not be reviewed or published.
Thanks.

REFEREE: Reviewer | **Revision** (0) 4 Jan 2020

Dear AE,
The authors showed the effects of orexin type 1 receptor antagonism on hematologic parameters in morphine-dependent rats, However, there are still several issues need to be revised in the paper:
1- Many typos and grammatical errors in the paper need to be carefully revised by the authors.
2- It seems that the structure of the material and methods section should be corrected. for example, it better than the drug introduction part to be the first part of this section, etc.
2- In the groups section. the number of the rats in each group mentioned 8, but in the description of each group, the number mentioned 7.
3- Some references are missed in the text.
4- The Relevant P-values should be mentioned in the results section.
5- In the results section. the effects of orexin type 1 receptor antagonism on eosinophil and lymphocyte, not described.
Thanks.

saeedeh salimi: Associate Editor | **Revision** (0) 4 Jan 2020

Dear EIC
The manuscript is an experimental study and its topic is in the scope of the journal. But it needs major revision especially in the following comment:
1- English language edition with a professional.
2- Adding the sham group in the study.
Best regards

REFEREE: EIC | **Revision** (0) 7 Jan 2020

Dear Author
The manuscript is an experimental study and its topic is in the scope of the journal. But it needs major revision especially in the following comment:
1- English language edition with a professional

2- Adding the sham group in the study.

Best regards

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Responses to reviewers

We are very grateful to the reviewers for their comments. We have improved our paper in the light of their useful suggestions. We hope our revision has improved the paper to a level of their satisfaction.

Reviewer 1:
In this manuscript, the authors found that orexin-A receptor antagonist SB-334867 could reduce several hematologic factors in morphine-depended rats, such as white blood cell count, platelet cell count and hematocrit. Several concerns are listed below.
1. In this manuscript, the authors set up 4 experimental groups, control, morphine alone, SB-334867 and SB-334867 with morphine. It would be better to add one more group in the experimental setup, treat the rats with morphine first, then add the receptor antagonist SB-334867. This will be more related to human study, people usually use morphine first, then you need to treat them. Please make sure all the Ns in each groups is correct. For example, the control group, they has 6 mice, but in the method part, the authors said 7 per group.

Undoubtedly, this group will spotlight the route to understand the effect of SB on hematologic factors in morphine-depended rats with much more profoundness as the respected reviewer has also recommended. We can do that in another research and compare pretreated and post-treated groups. At the moment we do not have any data about it and have not SB to do that.
We checked the Ns throughout the paper and corrected them in experimental groups.

2. The authors mentioned in the DATA ANALYSIS part, morphine withdrawal symptoms, How did increased/ reduced MCHC, WBC, and platelet cells count related to morphine-withdrawal symptoms?In current study we studied the effect of pretreatment of SB on morphine dependency to find the effect of this drug on dependence not withdrawal behaviors.So, we corrected it at the first sentence of data analysis.

3. How does this research apply to clinical study?In this study we wanted to find the effect of orexin inhibition in morphine dependency. Because the effect of SB in treatment of morphine dependency has proven in many previous

behavioral and electrophysiological studies (as the following) and on the other hand, as current study shows the morphine has some effects on hematologic factors so we investigated the effect of orexin blockade on hematologic factors in dependent state:

1. Neurosci Lett. 2014 Aug 22;578:90-4. doi: 10.1016/j.neulet.2014.06.038. Epub 2014 Jun 24.by Mousavi. Y et al.

2. Neurosci Lett. 2017 Jan 1;636:276-281. doi: 10.1016/j.neulet.2016.10.051. Epub 2016 Nov 2. By Hooshmand et al.

4. Please go through the manuscript and correct misspellings.The whole manuscript reviewed by a native English speaker.

Reviewer 2:

I read your manuscript carefully and I think your subject has enough appeal to print in the journal but it has some structural and other problems that you must answer to them.

• The basic problem is about your study design that you did not have sham group; Since At first you should demonstrate statistically that there was no significant difference between your sham and vehicle groups and then compared other groups with these. So if you could correct this problem, your work will be defensible and judgmental, otherwise it will not be reviewed or published.

As experimental groups and results show we added the sham group (naïve rats).Because there was not significant difference between naïve and vehicle-treated rats (Control), therefore, we did not show the naïve rats in figures. Therefore, the comparison between sham group ratsand saline-treated ones has been shown in table 1.

Reviewer 3:

Authors showed the effects of orexin type 1 receptor antagonism on hematologic parameters in morphine-dependent rats, However, there are still several issues need to be revised in the paper:

1- Many typos and grammatical errors in the paper need to be carefully revised by the authors.The whole manuscript reviewed by a native English speaker.

2- It seems that the structure of the material and methods section should be corrected. for example, it better than the drugs introduction part be the first part of this section, etc.Attempt was made to correct the structure of the material and methods section.
2- in the groups' section. the number of the rats in each group mentioned 8, but in the description of each group, the number mentioned 7.We checked the Ns throughout the paper and corrected them in experimental groups.

3- some references are missed in the text.We added the missed references as has shown.
4- the Relevant P-values should be mentioned in the results section.We mentioned the P valuesthroughout the paper.
5- in the results section. the effects of orexin type 1 receptor antagonism on eosinophil and lymphocyte, not described.We explained it at the 3rd paragraph of the results section.

Associate Editor's Comments:

1- English language edition with a professional

The whole manuscript reviewed by a native English speaker.

2- Adding the sham group in the study.

As experimental groups and results show we added the sham group (naïve rats).Because there was not significant difference between naïve and vehicle-treated rats (Control), therefore, we did not show the naïve rats in figures. Therefore, the comparison between sham group rats and saline-treated ones has been shown in table 1.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

saeedeh salimi: Associate Editor | **Revision** (**1**) 24 Mar 2020

Dear EIC,
The manuscript has been revised carefully according to the comments of reviewers, but it needs minor English language revision.
Best regards

REFEREE: EIC | **Revision** (**1**) 4 Apr 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Response to Associate Editor 1

We are very thankful to the Associate Editor for comment. We hope our revision has improved the paper to a level of your satisfaction.

Associate Editor 1:
Dear editor
The manuscript has been revised carefully according to comments of reviewers, but it needs minor English language revision.
The whole manuscript reviewed by a native English speaker.

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision** (2) 15 Apr 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.