September 10, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4995-review.doc).

Title: Antinociceptive effects of novel melatonin receptor agonists in mouse models of abdominal pain

Author: Chunqiu Chen, Jakub Fichna, Moshe Laudon, Martin Storr

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4995

The manuscript has been improved according to the suggestions of reviewers:

Reviewed by 01213502

However, there is an important concern to me: The authors used the percentage of control (numbers of pain-related behaviors) instead of true numbers. It may not be reliable. For example, if the study group responded 3 pain-related behaviors compared to 4 pain-related behaviors of the control group .There may have 25% down but only 1 different behavior. Suggest the authors used true numbers of the 「pain-related behaviors」 for statistics.

We would like to thank the Reviewer very much indeed for this valuable comment.

The methods for characterizing the antinociceptive action of various compounds in mice based on their behavioral response to intracolonic administration of mustard oil (MO) and capsaicin or intraperitoneal injection of acetic acid solution are well established and very often used and published.

These models have also been adapted in our laboratory and widely used when describing the antinociceptive activity of several classes of potential therapeutics. However, in our laboratory the conditions of the assays have been set so the number of behaviors is relatively high, while still accepted by the local animal committee.

Typically, the number of behaviors in MO-treated mice is 60-70, while in capsaicin- and acetic acid solution-treated mice 30-40. In these conditions even slight changes in the number of behaviors (caused by either anti- or pro-nociceptive action of studied compounds) can be noticed, but simultaneously only significant and pharmacologically relevant action is reflected by statistically significant changes in obtained values. Therefore, the situation described by the Reviewer is unlikely.

Also for the reason of presenting pharmacologically relevant data, some other behavioral models of pain have not been used in the study.

For the above mentioned causes we believe that there is no need to represent true values. However, the description provided above has now been provided in the Methods section of the manuscript.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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