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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77340

Title: Bladder-colon chronic cross-sensitization involves neuro-glial pathways in male mice

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03948836
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor, Research Assistant Professor
Reviewer's Country/Territory: China
Author's Country/Territory: France

Manuscript submission date: 2022-05-31

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-06-07 05:18

Reviewer performed review: 2022-06-08 14:22

Review time: 1 Day and 9 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The author built up a chronic cross-organ visceral sensitization model in this study and investigated the mechanisms involved in the bladder-colon cross-sensitization. As a result, they proved that intravesical injections of acetic acid induce a long-lasting colorectal hypersensitivity to distension. And this hypersensitivity was mediated by neuroglial interactions, MAPK-p38 phosphorylation, and the NK1 receptor. The paper is well written and contributes a stable mice model for chronic cross-organ visceral sensitization. However, authors should consider the following issues: 1. A mouse model of chronic bladder-colon cross-sensitization was established in mice via ultrasound-guided intravesical injections of acetic acid. And authors evaluated colonic nociceptive response at hour 1, day 1, and day 7. It is insufficient for chronic symptoms, and the authors had mentioned in limitation. However, whether the sensitization of the bladder changed? 2. In the method paragraph, the authors mentioned that "bladder and distal colon samples were removed at Days 3 and 7"(page 9, row number 250-251). However, we can not find the result of Day 3 in Figure 2. 3. In figure 6, the western blot bars were edited. Although the authors had explained that "Samples were run on separate gels and compiled for figure". Why samples can not run together? The authors also did not provide the images of GAPDH. To explore the effect of CP 99994 injection on phosphorylated MAPK-p38, the expression of total MAPK-p38 in the different groups should be assessed. Furthermore, CP 99994 was used as an NK1R antagonist in this study, but the authors did not verify the effect of CP 99994 on the NK1R expression or biological activity. The same issues were found in Figure 7. 4. What is the relationship between NK1R and phosphorylated MAPK-p38? The author mentioned that "This

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receptor would activate, directly or indirectly, the MAPK-p38 protein via its phosphorylation (P-p38)". Then, SB203580, a MAPK-p38 inhibitor, could influence the expression of NK1R. Why? 5. The number of microglia cells in the spinal cord did not change in the mouse model of chronic bladder-colon cross-sensitization. However, the minocycline, a microglial inhibitor, was applied in this study. How does it make sense? We suggest evaluating the activation of microglia. Not only the quantity. 6. Neural activation in the dorsal horn of the spinal cord L6-S1 was assessed by c-Fos immunofluorescence. However, no representative immunofluorescence picture was presented in figure 3. And this is more powerful in explaining the increase in neural activation.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05395205
Position: Peer Reviewer
Academic degree: MD, PhD

Professional title: Doctor, Postdoc

Reviewer's Country/Territory: China

Author's Country/Territory: France

Manuscript submission date: 2022-05-31

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2022-07-08 11:39

Reviewer performed review: 2022-07-08 12:15

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors developed a new model of cross-organ visceral sensitization between the bladder and the colon in mice and investigated the mechanisms involved in this disease model. Some concerns and suggestions are listed as below: 1. Only adult male wild type C57Bl/6 mice were used in this study. However, emerging data has convincingly demonstrated the existence of sex-dependent structural and functional differences of rodent microglia (Uncovering sex differences of rodent microglia, J Neuroinflammation. 2021). Additional experiments are needed. 2. In Figure 1, apart from saline and acetic acid groups, an important healthy control group is missing. 3. Area under the curve shoud be shown. 4. In Figure 2 (Bladder and colorectal permeabilities and inflammation), how about other time points? 5. How will you define that this model is successful, representing the chronic cross-organ visceral sensitization? 6. Quantification of c-Fos immunoreactive cells at different time points and regions should be provided. 7. In Figure 4, specific microglial markers such as Tmem119 and Iba1 should be used. 8. In Figure 4, how about microglial morphology between groups? 9. I wonder if the effect of minocycline injection at the central level on visceral sensitivity is dose-dependent. 10. Colony-stimulating factor 1 receptor (CSF1R) inhibition/withdrawal approach should be used to confirm the findings.

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77340

Title: Bladder-colon chronic cross-sensitization involves neuro-glial pathways in male mice

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05395205
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Doctor, Postdoc
Reviewer's Country/Territory: China
Author's Country/Territory: France

Manuscript submission date: 2022-05-31
Reviewer chosen by: Han Zhang
Reviewer accepted review: 2022-10-10 14:20
Reviewer performed review: 2022-10-10 14:26
Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors did not perform any additional experiments to address the concerns from the reviewers.