

May 10, 2018

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Dear Dr. Fang-Fang Ji and Reviewers:

We thank the referees and Section Editor for their thorough and careful review of our manuscript entitled “Targeting increased levels of tumor necrosis factor (TNF) in the brain relieves neuropathic pain” (**Manuscript NO.:** 39078, **Column:** Review).

The editorial suggestions you had indicated in the manuscript have been incorporated; the recent edits have been indicated by yellow highlighting for easy identification. The word content for the Abstract and the manuscript remains within the allowable limit based on the journal guidelines.

We thank the reviewers for their insightful comments and suggestions to improve our manuscript. The authors believe that the revised manuscript satisfies all of the reviewers' comments, and clearly addresses an area of research the reviewers deemed interesting and important. We thank the Editor for allowing us the time and opportunity to respond to the reviewers' comments, and look forward to sharing our opinions and research findings with the scientific community through publication in **World Journal of Anesthesiology**.

Responses to reviewers suggested revisions:

Reviewer's code: 02488181. The review article is comprehensive and worth of publishing in WJA. The reviewer has only one minor suggestion. It would be good to have a summarized table to describe the mechanisms of action of TNF signaling in the brain and corresponding therapeutic strategies.

Reply: As a minor suggestion we have considered a table. However, we are presently preparing an extensive publication consisting of new discoveries and where we are preparing such a table. Therefore, since this was not in the scope of the present review, and to avoid redundancy, we refrained from adding such a table to the current manuscript.

Reviewer's code: 00529915. Following points are suggested to improve the manuscript. 1. Mention an example in the core tip that how the TNF practically (drug or therapy) can be targeted? 2. Slightly rephrase or reorganize relevant parts of your manuscript so that an average reader who is not specialist in the field can understand the practical differences in treatment according to your suggestions as compared to the classic approach of treatment of neuropathic pain. 3. Please modify the title and make it more general like "TNF and neuropathic pain" etc

Reply: 1) A sentence has been added to the core tip providing an example of how TNF can be targeted: “TNF can be practically targeted by non-invasive delivery of anti-TNF biologics directly to the ventricles of the brain via perispinal injection.” Due to the addition of the previous sentence to the Core Tip, this section now slightly exceeds the guideline limit of 100 words (now at 115 words). 2) We have slightly rephrased or reorganized relevant parts of our manuscript on pages 14-16. 3) The main title of the manuscript has been edited to: “Targeting tumor necrosis factor (TNF) in the brain relieves neuropathic pain”, and a more general running title has been added to the manuscript: “TNF and neuropathic pain”.

Reviewer’s code: 02484487. This article is informative but most of the research is done on targeting peripheral TNF and very less work is done on Brain TNF which needs further research. It is still a hypothesis regarding brain TNF and neuropathic pain but explanation is good and will definitely help the readers. Human studies are still lacking so if any research done on humans will add further information.

Reply: We have included the work of Dr. Tobinick, the pioneer of non-invasive perispinal delivery of etanercept to block TNF levels in the human brain. Specifically, this study used perispinal delivery of etanercept to treat patients experiencing discogenic pain. We have published several papers with Dr. Tobinick. In addressing your suggestion, we have added one of these publications, which is a case study that used perispinal delivery of etanercept (a TNF blocker) to treat neurological dysfunction, including pain, induced by a previous traumatic brain injury (see new reference #88 and text on pages 15 and 16).

Reviewer’s code: 00041963. “choronic” could be added as a key word.

Reply: The word ‘chronic’ has been added as a key word.

Thank you for your time and effort in reviewing this manuscript and for your constructive comments, which we feel served to improve the manuscript.