Dear editor,

Please find attached files of revised manuscript in word format

Title: Nitrergic Neurons Involvement in the Colonic Motility in Rat Model of Ulcerative Colitis

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Thanks very much for taking your time to review this manuscript. We really appreciate all your generous comments and suggestions! Please find my itemized responses in below and my revisions in the re-submitted files:

Reviewer #1:

Dear Editor, Thanks to the authors for this good-organised experimental study. The abstract summarizes and reflects the work described in the manuscript. The manuscript adequately describes the background, present status and significance of the study. The manuscript interprets the findings adequately and appropriately,

highlighting the key points concisely, clearly and logically. Also, the figures, diagrams and tables are sufficient, good quality and Despite the small number of cases, I think that the current study will contribute to the literature.

Reviewer #2 :

This is an interesting experimental work showing that colon-located nitrergic neurons play a role in the pathophysiology of colitis. Concerns: 1. Please use the term "nitrergic" consequently (in the core tip it´s nitrogenous). 2. Please correct the phrase : the etiology of UC generally remain... (should be remains). 3. Naturally, you have employed an antibody generated against neuronal nitric oxide synthase. However it is known that neurons in the colon may also express endothelial NOS (and possibly even iNOS): So, my question is: Do you have any information, if these non-neuronal NOS isoforms play any role in colitis?

Thank you for your advice. We are very grateful to your comments for the manuscript. According to your advice, we amended the relevant part in manuscript. All of your questions were answered one-by-one. 1. The word "nitrogenous" in core tip has been completely replaced with "nitrergic". 2. "The etiology of UC should be remains complex, however its pathogenesis might be related to the genetic, immunological, psychiatric depression & anxiety, environmental, dietary allergy, intestinal flora, and other factors." the sentence has been corrected. 3. As the rate-limiting enzyme of NO synthesis in the body, NOS has three sub-types: iNOS, eNOS and nNOS. Histological studies have identified intense focal iNOS expression by the inflamed bowel

epithelium and in the mononuclear cell infiltrate in the intestinal tissues of both Crohn's disease and UC patients [1]. A great number of studies suggest that iNOS in ENS may play a part in preventing activation of mast cells, reducing leukocyte adhesion to endothelium, and protecting the host from being invaded by colonic bacteria [2-4]. In normal and UC states, eNOS expression is limited to colonic vascular endothelium [5]. Baker *et al*. [6]confirmed that during DSS induced UC, eNOS KO mice suffered less tissue damages and inflammations than wild-type mice, suggesting that eNOS is essential for maintaining the integrity of gastrointestinal mucosa. nNOS is one of the specific markers for the nitrergic neurons within the ENS, and the primary inhibitory neurons of the colonic MP [7]. By releasing inhibitory neurotransmitter NO, nitrergic neurons can regulate gastrointestinal motility. The changes in expression of nNOS in colonic MP of UC rats indicate that nitrergic neurons may be involved in NO-based neurotransmission and regulate gastrointestinal motility in UC state. Therefore, we mainly studied nNOS and nitrergic neurons.

Thank you and all the reviewers for the kind advice again. If you have any questions, please contact us without hesitate.

Yours sincerely,

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