

RESPONSE TO REVIEWERS' COMMENTS

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Title: Molecular signalling during cross talk between gut brain axis regulation and progression of irritable bowel syndrome: A comprehensive review

The authors of this manuscript express their sincere thanks to the Editor-in-Chief and the reviewers for the critical assessment of this work. The authors have acted upon the recommendations of the Editor-in-Chief and the reviewers which have resulted in a significant enhancement in the quality of this manuscript. **All modifications suggested by reviewers have been incorporated in the revised manuscript and shown in red colour.** Response to the comments is outlined below.

Reviewer #1:

General comment: The present review article by Singh et al is mainly focused on the crosstalk between gut and brain and its axis, in patients with irritable bowel syndrome (IBS). The review is well written and the topic was analyzed in depth.

Response: We are deeply encouraged by the reviewer's generous comments about the quality of our work. Thanks a lot for reviewing and considering our article for publication in the journal.

Comment: My only observation is that Authors focused their attention mainly on dopamine and serotonin. However a mention to histamine is necessary, since it has been observed an increased mastocyte infiltration and degranulation close to sensitive nerves in IBS population (see Barbara G et al, Gastroenterology 2007).

Response: We have incorporated the essential details regarding the histamine role in IBS at the suitable place on page 14-15 of the manuscript (highlighted in red). Further, Barbara G et al, Gastroenterology 2007 has been cited in the manuscript and incorporated as reference no. 134.

Comment: Minor issues: 1) In the legend of figure 1 there are some acronyms that have not been fully explained (ANS, HPA, ECC, ICC, SMC). 2) cajal - - >Cajal.

Response: (1) The acronyms have been explained in legend to Figure 1 abbreviations (ANS - autonomic nervous system; HPA - hypothalamic–pituitary–adrenal axis; ECC - Enterochromaffin cells; ICC - Interstitial cells of Cajal; SMC – Smooth muscle cells; SCFAs – Short chain fatty acids) as well as at the suitable place in the manuscript.

(2) Cajal is the name of scientist who first described Interstitial cells of Cajal (ICC) that represent a particular network formed by some peculiar cells.

Reviewer #2:

General comment: This review focused on the role of brain-gut-microbiota axis in the irritable bowel syndrome. The review stressed the role of microbiota in the gut-brain interactions. Besides, role of signal transducing cells such as enterochromaffine cells (EC) and dendritic cells (DC) has also been illustrated. Then the author gave a detailed presentation of IBS pathogenesis.

Response: We are thankful to reviewer for generous comments about the manuscript.

Comment: 1) Though interesting, the review had several limitations. 1) the structure of the review should be improved. In my opinion, the author should give an illustration about IBS first, and then focus on the role of brain-gut-microbiota axis in the pathogenesis of irritable bowel syndrome.

Response: The review has been restructured and modified as suggested. IBS has been elaborated in detail in beginning after introduction section followed by brain-gut-microbiota axis. Section headings are highlighted in red.

Comment: 2) the review should have a specific topic. For example, in this review, the author talked about the genetic constructions of IBS, which seemed have no association with the brain-gut-microbiota axis.

Response: We are thankful to reviewer for constructive suggestion. Accordingly in the revised manuscript, we have deleted the text related with genetic constructions of IBS and the associated references.

Comment:3) Some figures, such as Fig. 2, are not very clearly presented.

Response: Figures have been redesigned for a clear presentation.

Additionally,

We have thoroughly checked the manuscript for typos and incorporated corrections. Further, we have also added a new reference “Singh *et al*” as reference no. 6. All changes are shown in red colour.

Names of two more authors (Aditya Kumar Yadav and Ramesh Kumar) have been incorporated in the authors’ list. They have contributed significantly in literature search during revision process and restructuring of the revised manuscript.