DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

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October 28, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format, (file name:13935-review.doc).

Title: Altered VIP expression in IBS Patients and rats with TNBS-induced colitis

Author: Arseima Y. Del Valle-Pinero, LeeAnne B. Sherwin, Ethan M. Anderson, Robert M. Caudle, and Wendy A. Henderson

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13935

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

1. Format has been updated
   a. Please find the addition of specific wording and formatting as requested (i.e., Name of journal, ESPS Manuscript NO: 13935 and Columns) [As highlighted in blue].
   b. We have made format modifications to the "Authors' department" as requested [Comment WL1].
   c. Please find the abstract structure modified into the recommended sections (i.e., Aim, Methods, Results, Conclusion) [Comment q2].
   d. Please find comment section revised per your attached revision policies as per your recommendations [Wang JL4].

2. Response has been made according to the suggestions of the reviewer:

(1) Are TNBS-induced colitis rats quite appropriate for an IBS model? Please discuss precisely.

The authors understand the question expressed by Reviewer 1 regarding TNBS as a comparative model for IBS. Current research supports the use of TNBS induced colitis in rats as a model that demonstrates persistent visceral and somatic hypersensitivity similar to those who suffer from functional gastrointestinal pain. TNBS rectally infused in rats has been found to result in intense colitis involving all muscle layers of the colon. This intense colitis has been reported to mimic a post-infectious IBS. Zhou et al. (2010) found TNBS-induced colitis resulted in chronic colonic hypersensitivity. This hypersensitivity has been found to persist in rats even with complete resolution of histological findings of colitis, similar to individuals who suffer from post-infectious IBS. Please find the addition of this justification in the text as requested. (Page 6, 1st paragraph)

(2) How do the authors discuss the differences in VIP gene expression and plasma VIP levels between IBS patients and healthy controls?

This question is of particular interest to the authors as well. The authors suggest that the differences in VIP gene expression and plasma VIP levels between those with IBS and healthy controls may be the result of the time-dependent, inherent chronicity of IBS. Changes in VIP gene expression have been shown to be affected by post-translational modifications and in turn affect other molecules upstream and downstream of the VIP pathway. To better elucidate the functional mechanisms of VIP in patients with IBS, the authors anticipate that through publication of these findings further studies will be warranted to provide additional studies with repeated longitudinal measures of VIP over time.

(3) It is unlikely that the pathogenesis of IBS depends only on VIP. How about the other gut hormones?

The Reviewer raises a good point. The authors agree it is important to consider the possibility there are numerous factors, potentially interacting with each other, which influence the development and persistence of IBS. We have now addressed this limitation in our discussion section. (Page 14, second to last paragraph)

Sincerely,

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