

October 18, 2013

Dear Editor,

Thank you for the comments on the previous version of our manuscript. Please forward our appreciation to the referees for their comments and constructive criticisms, which we believe have improved the manuscript considerably

Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

Title: Abnormal endocrine cells in the ileum of patients with irritable bowel syndrome

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5482

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

Point-by-point response to the reviewers

I. Reviewer 00843082

1. As regard the morphometric quantification of the endocrine cells we agree in principle with the reviewer. The densities of cells measured in the present study are relative densities and are not absolute densities. This approach was introduced by

Weibel E. and Elias H in 1967 and Weibel et al. in 1969 (Weibel E. and Elias H. Introduction to stereologic principles. In: Weibel E. and Elias H (eds), quantitative methods in morphology, Springer-Verlag, Berlin. pp 89-98./ Weibel et al. J Cell Biol 1969;42:68-91). This approach made morphometric quantification easier to perform. In 1997, using this mathematical principle, we developed and evaluated a method to quantify the endocrine cells in relation to the area of the epithelium and expressed as the number of endocrine cell in 1mm² of the epithelium (El-Salhy et al. Application of computer image analysis in endocrine cell quantification. Histochem J. 1997;29(3):249-56). This method of quantification is generally accepted and we used it in a large number of publications including publications in World journal of Gastroenterology. Using Weibel principles, other researcher express the number of endocrine cells in relation to 100 epithelial cells or to the number of crypts/villi. We prefer, however, to use the method that we evaluated and worked with under several years.

To clarify this point as the reviewer recommended in page 8 and references 36 and 37 were added.

2. We thank the reviewer for raising such an interesting point. We have proposed an assumption for the reduction of serotonin cells as being an abnormal differentiation from stem cells as suggested by the reviewer on page 12 and 13 and references 41-59 were added.

II. Reviewer 00004290

1. The endocrine cells in the colon of IBS patients have been investigated and published by us previously (El-Salhy et al. Dig Dis Sci 2012; 57:723-731). Comparison between the results of the ileum and colon is provided in page 11.

2. The method used in quantification is commented upon in 1 to the reviewer I.

3. We discussed serotonin and TPH-1 in relation to visceral hypersensitivity in page 13 as suggested by the reviewer and references 62-64 were added.

III. References and typesetting were checked according to the journal style

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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