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Fax: +1-925-223-8243
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Format for ANSWERING REVIEWERS

June 22, 2018

Dear Editors,

We would like to thank the editors and the reviewers for consideration of our submitted paper and for a critical appraisal of the manuscript.
Please find the attached edited manuscript (File name: 39873-Edited Manuscript) with the changes that have been suggested by the reviewers.

Title: IMPLICATION OF NEUROHORMONAL COUPLED MECHANISMS OF GASTRIC EMPTYING AND PANCREATIC SECRETORY FUNCTION IN DIABETIC GASTROPARESIS.

Authors: Bashair Mussa, Sanjay Sood, Anthony J.M. Verberne

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 39873

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Major Points

Reviewer point # 1: Excellent reviews on DGP or related original articles have been published. The authors are recommended to refer to them and emphasize the importance of a neurohormonal interrelationship between the gastric emptying and pancreatic secretory function more. Examples 1) Am J Gastroenterol 2013; 108:18–37; doi:10.1038/ajg.2012.373; published online 13 November 2012 2) Chinmay S. Marathe, Christopher K. Rayner, Karen L. Jones & Michael Horowitz (2016) Novel insights into the effects of diabetes on gastric motility, Expert Review of Gastroenterology & Hepatology, 10:5, 581-593, DOI: 10.1586/17474124.2016.1129898 3) Br Med Bull. 2013; 105: 213-30. doi: 10.1093/bmb/ldt003. Epub 2013 Jan 29. 4) Gastroenterology Clinics of North America Volume 44, Issue 1, March 2015, Pages 39-57

Author Response: Done. The recommended references were added to enhance the quality of the review.

"*Reference 1) Am J Gastroenterol 2013; 108:18–37; doi:10.1038/ajg.2012.373; published online 13 November 2012*" was added to the first paragraph in the introduction section.

"*Reference 2) Chinmay S. Marathe, Christopher K. Rayner, Karen L. Jones & Michael Horowitz (2016) Novel insights into the effects of diabetes on gastric motility, Expert Review of Gastroenterology & Hepatology, 10:5, 581-593, DOI: 10.1586/17474124.2016.1129898*" was added to the second paragraph in the introduction section.

"Reference 3) Br Med Bull. 2013; 105:213-30. doi: 10.1093/bmb/ldt003. Epub 2013 Jan 29" was added to the first paragraph in section 3.1 which titled "Extrinsic control of gastric emptying and pancreatic secretion"

"Reference *4) Gastroenterology Clinics of North America Volume 44, Issue 1, March 2015, Pages 39-57*" was added to the first paragraph in the introduction section.

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Minor Points

Reviewer Points # 1: It is hard to understand what "the latter"s mean. (especially lines, 292, 479, 549, 584 and 587)

Author Response:
The word "latter" was used to avoid repeating the same term several times. However, as it has been requested "the latter" now is replaced with the original terms in the following lines (292, 479, 549, 584 and 587). In addition, "the latter" in line 158 is replaced with "ICCs and myopathy".

Reviewer Point # 2: Generally speaking, "recent" and "recently" usually refer to the last few years.

Author Response: The word recent/recently has been changed as follow:

Line 243 (recent evidence replaced with a strong evidence)
Line 588 (recent studies is replaced with studies in animals)
Line 649 (recently is deleted)
Line 665 (recent research is replaced with previous research)

Reviewer Point #3: Please cite a reference on the latency of pancreatic responses to nutrients stimuli at appropriate place (line 219).

Author Response: Done. The following reference was added "Singer MV, Solomon TE, Wood JD, Grossman MI. Latency of pancreatic enzyme response to intraduodenal stimulants. *American Journal of Physiology* 1980; **238**: G23-G29".

Reviewer Point #4: Detailed descriptions on gastric emptying cannot be confirmed in ref 31 and 32 (line 237). Ref 31 is textbook.

Author Response: The following references were added to give more detailed description on gastric emptying:

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1. "Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Compr Physiol* 2014; **4**(4): 1339-1368".
2. "Vanormelingen C, Tack J, Andrews CN. Diabetic gastroparesis. *Br Med Bull* 2013; **105**: 213-230".

Author Response: Reference 31 is a comprehensive chapter about the central autonomic control of the pancreas. It is one of 20 chapters in a text book titled "Central Regulation of Autonomic Function". We cited this chapter because it includes important information for the reader.

Reviewer Point #5: Please describe the reason why the authors determined "these reflexes seem to be mainly mediated by GI hormones". The reasonable reason of "mainly" (line 243)

Author Response: Done. The word "mainly" was deleted so that the sentence is more accurate.

Reviewer Point #6: Please paraphrase "unmasks" to another word. It is difficult to get meaning (270)

Author Response: Done. "Unmasks" has been replaced with "indirectly enhances"

Reviewer Point #7: It is difficult to get meaning (line 308-311)

Author Response: the following statements have been changed to be more meaningful "As mentioned previously, CCK and 5-HT are powerful pancreatic secretagogues and so their effects on DMV PPNs have been tested. The results showed that all DMV preganglionic neurons that were antidromically activated in response to stimulation of the pancreatic branch of the vagus nerve had similar axonal conduction velocities in the C-fibre range. This is not surprising since most of the subdiaphragmatic vagal efferents are unmyelinated"

The new statements are as follow "As mentioned previously, CCK and 5-HT are powerful stimulatory agents of the pancreatic secretion therefore their effects on DMV

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PPNs have been investigated. The results of this investigation has showed that all DMV preganglionic neurons, the origin of the pancreatic vagal efferent, were activated in response to stimulation of the **pancreatic** branch of the vagus nerve and had axonal conduction velocities in the C-fibre range. This is not surprising since most of the subdiaphragmatic vagal efferents are of C-fibre type.

Reviewer Point #8: Recently it is reported that TRPV2 ion channel is involved in LPI-stimulated GLP-1 secretion in enteroendocrine L cells. (line 4.1.1) Ref Lysophosphatidylinositol-induced activation of the cation channel TRPV2 triggers glucagon-like peptide-1 secretion in enteroendocrine L cells http://www.jbc.org/content/early/2017/05/22/jbc.M117.788653

Author Response: Done. The following statement along with the reference were added "Interesting findings have demonstrated the involvement of transient receptor potential channel vanilloid 2 (TRPV2) ion channel in Lysophosphatidylinositol-induced GLP-1 secretion from enteroendocrine L cells".

Reviewer Point #9: Recently it is reported that a mechanosensitive TRPV2 ion channel is co-expressed in nNOS-expressing inhibitory motor neurons in mouse stomach (line 530) Ref TRPV2 ion channels expressed in inhibitory motor neurons of gastric myenteric plexus contribute to gastric adaptive relaxation and gastric emptying in mice https://www.physiology.org/doi/abs/10.1152/ajpgi.00256.2012?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

Author Response: Done. The following statement along with the reference were added "In addition, recent reports have shown that mechanosensitive TRPV2 ion channel is co-expressed in nNOS-expressing inhibitory motor neurons in mouse stomach emphasizing the contribution of these inhibitory neurons gastric adaptive relaxation and gastric emptying in mice"

Reviewer Point #10: "GI emptying" may be replaced to Gastric emptying ? (line 564)

Author Response: Done. GI emptying has been replaced with Gastric emptying)

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Reviewer Point # 11: Line 729, ref 17

Author Response: Done. The reference has been edited

Reviewer Point # 11: Line 1038, ref 132. There is no published year.

Author Response: Done. The year has been added to the reference.

Reviewer Point # 13: Line 136, ref 136. There is unnecessary "." And ",".

Author Response: Done. The unnecessary punctuation marks were removed.

Reviewer Point # 14: Figure1. The direction of a distal side of two arrows in vagal afferents should be toward NTS but not to stomach and pancreas.

Author Response: Viscerosensory vagal afferents are originated from pseudo-bipolar neurons of the nodose ganglion and project in a bidirectional fashion to the nucleus of the solitary tract (NTS) in the brainstem and peripherally to different regions of the GI tract (e.g. Pancreas and Stomach). This is the reason for having bidirectional arrows in Figure 1.

The comments of the reviewers improved the manuscript, significantly.

Thank you for considering our manuscript for publication in the *World Journal of Gastroenterology*.

Yours Sincerely,

Dr. Bashair Mussa
Department of Basic Medical Science
College of Medicine
University of Sharjah
Sharjah-UAE