Jin-Xin Kong
Science Editor, Editorial Office

07 August 2016

Dear Dr Jin-Xin Kong,

Thank you very much for taking the time to review our paper '**GLP-1 in the pathophysiology and pharmacotherapy of clinical obesity**' and for the constructive criticism offered.

Reply to reviewers

To reviewer 00058872

'Authors should stress this main point, i.e., Behavioural interventions that deal with both diet and physical activity show small but significant benefits on weight loss maintenance. BMJ. 2014 May 14;348:g2646.'

Thank you for this helpful suggestion, we have now added a sentence about this into the revised manuscript and quoted the suggested reference.

> Lifestyle intervention, in the form of dietary, behavioural and exercise counselling, are currently the suggested first line treatment for obesity [20]; however, whilst a recent meta-analysis reports such interventions to show small but significant benefits on weight loss maintenance[21], weight loss achieved and sustained with lifestyle intervention alone remains suboptimal[22-24].

To reviewer 00506276

'This is an interesting, detailed and well-written review article. It will provide a lot of information for basic researchers and clinicians interested in endocrinology, diabetes and obesity. I have no critical comments.'

Thank you for your positive comments they are much valued.

To reviewer 00506250

'Author presented GLP-1 in the pathophysiology and pharmacotherapy of obesity in review article. I believe this review article is excellent. The figures in manuscript are very easily understandable. Paper is very in detail but clearly written.'

Thank you for your positive comments.

'I noted only minor concern. In, P8, L3 "The early phase of GLP-1 secretion is likely to be neutrally mediated with roles for the parasympathetic vagal nerve and neurotransmitters such as gastrin-releasing peptide (GRP) and acetylcholine (ACh)". However, recent evidence suggest that L cells exist in the upper intestine, which may be responsible for this rapid elevation of GLP-1, although the numbers of L cells are much higher in lower intestine (1, 2) 1. Holst JJ. The Physiology of glucacon-like peptide 1. Physiol Rev 2007; 87: 1409-1439. 2. Pais E, Gribble FM, Reimann F. Stimulation of incretin secreting cells. Ther Adv Endocrinol Metab 2016; 7: 24-42. This evidence also may be commented.'

We have added these concepts into the revised manuscript and referenced the papers suggested:

> The early phase of GLP-secretion has traditionally been attributed to signals from the parasympathetic vagal nerve and neurotransmitters such as gastrin-releasing peptide (GRP) and acetylcholine (ACh). However, more recently, GLP-1 secreting cells that show direct secretory responses to nutrient stimulation [83] have been localised in significant numbers in the proximal small intestine[84][85] implicating a role for this albeit sparser population of

proximal GLP-1 releasing cells in the rapid postprandial rises of plasma GLP-1.

To the editor,

We have attached some of the documents listed below, although for some we were unsure what to attach.

1 27734-Revised manuscript - attached
2 27734-Answering reviewers - attached
3 27734-Copyright assignment - attached
4 27734-Audio core tip – added to Abstract page
5 27734-Conflict-of-interest statement – added to Title page
6 27734-Google Scholar – we are no sure what to attach
7 27734-CrossCheck – we are no sure what to attach
8 27734-Grant application form(s) – we are no sure what to attach
9 27734-Language certificate – as one of us is a native English speaker we are no sure what to attach

We hope that our manuscript is now acceptable for publication.

With kindest regards,

Ananthi Anandhakrishnan and Márta Korbonits