Author’s response to reviews

Title: Glucagon-Like Peptide Receptor Agonists Attenuate Advanced Glycation End Products-Induced Inflammation in Rat Mesangial Cells

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Author’s response to reviews:

Dear Editors:

We are submitting the revised manuscript PHAT-D-17-00069 for consideration for publication in the BMC Pharmacology and Toxicology.

We appreciate very much the reviewers’ comments. We use the RED FONT to indicate the revised portions of the manuscript. We think that the manuscript has improved substantially after the revision.

Our point-by-point responses to the reviewers were included in the following pages.
Thank you in advance for your assistance in processing our manuscript.

Sincerely,
Jyh-Gang Leu, M.D., Ph.D.
Professor in School of Medicine
2017/08/05

To reviewer #1:

Specific comments:

1. Thanks for the reviewer’s comment. That is a very important point needed to be discussed. Therefore, we have cited the recent paper by Dr. Yang and discussed in the final part of that section. In page 15 lines 8-11, we have added the following sentences’’ SREBP-1c/Caveolin-1 signaling was proved to involve in PPARδ-regulated GLP-1R expression and GLP-1R-dependent Akt/bcl-2 signaling were related to PPARδ agonist treatment in pancreatic beta cell [29]. We suggest that PPARδ agonist downstream signaling may correlated to GLP-1R signaling in kidney cell. ‘’

2. We agree with the reviewer that mesangial cells used in this study should be addressed. We have added the sentences in Introduction first section, in page 3 lines 9-13, ‘’Mesangial cells increased fibronectin production and decreased proliferation in growing on AGE-modified matrix protein. Mesangial matrix expansion is one characteristic of diabetic nephropathy [6]. The anti-RAGE and anti-inflammatory therapies in mesangial cell may prevent the progression of diabetic nephropathy. ‘’

3. We agree with reviewer that effects of AGEs on GLP-1 and PPAR delta expression should be discussed. Therefore, we have added the sentences in Discussion first section ‘’In our study, the inhibitory of RAGE expressions by exendin-4 and L-165,041 incubation were reversed by siRNA of PPARδ treatment. We suggest that AGE may not only induce the RAGE expressions but also PPARδ expressions in RMC. ‘’
4. Thanks for the reviewer’s comment. Figure 3B and Figure 4 are our Western blotting results.

To reviewer #2:

We agree with the reviewer that GLP-1 peptide study in human mesangial cells is very important. We have added the sentences in discussion final section. In page 15 lines 19 to next page lines 1 ‘‘However, the downstream signaling and effects of GLP-1 peptide treatment in human mesangial cells should be more studied.’’

We have added the N=6 in each figure legend and stated the statistical test in Statistical analysis section in Methods (page 9 lines 15 and page 10 lines 1-4). Furthermore, we must apologize about our grammar errors and we had corrected in the revised manuscript.