Author’s response to reviews

Title: Effects of Radix Linderae extracts on a mouse model of diabetic bladder dysfunction in later decompensated phase

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Author’s response to reviews:

Dear Dr. Deepa Nath and Dr. Emily Wollmuth

On behalf of my co-authors, we appreciated editors and reviewers very much for giving us the comments to improve our manuscript entitled “Effects of Radix Linderae extracts on a mouse model of diabetic bladder dysfunction in later decompensated phase” (Manuscript Number: BCAM-D-18-00975). We revised the manuscript in accordance with reviewers’ comments, and carefully proof-read the manuscript. The main corrections in the paper and the responses to the comments are as following:
1. Yoshihiko Ito, Ph.D. (Reviewer 4):

The authors investigated the effect of Radix Linderae extracts on diabetic bladder disfunctions and alteration of bladder function on diabetic mice. This manuscript seems interesting. However, there are some errors and lack of information in the manuscript and the authors need to clarify following questions and concerns.

1.1 – Although authors performed single CMG, Continuous CMG is general. Why was single CMG used? Please discuss the limitation or reason.

Our response: Thank you for your comments, and this is an excellent suggestion to improve the quality of our paper. In this study, we have obtained the reliable data from the single CMG to reflect the functional change of diabetes bladder and prove the therapeutic effects of Radix Linderae (RL) on DBD. Besides, the single CMG has been used in our laboratory for a long time, since the high-efficiency. And some articles have been published, such as “Effect of SQW on the bladder function of mice lacking TRPV1” [1] and “Effect of the Chinese traditional prescription Suo Quan Wan on TRPV1 expression in the bladder of rats with bladder outlet obstruction” [2]. Also, we recognize the limitations of single CMG through your suggestion. We are willing to follow your method in the future experiments. And we discussed the limitation of single CMG in the manuscript as follow (Discussion, page 10, line 29-30 to page 11, line 1-3).

In addition, in this study, we have obtained the reliable data efficiently from the single cystometrogram (CMG) to reflect the functional change of diabetes bladder and prove the therapeutic effects of RL on the later phase of DBD. At the same time, we also realized that continuous CMG can provide more comprehensive and detailed data.

1.2 - Is pressure unit correct in figure 2? I think 10 cmH2O is reasonable.

Our response: Thanks for your comments, and we have found the error in the figure 2, which has been corrected in the revised manuscript.

1.3 - In the contraction response section, authors discussed that decrease of muscarinic receptor expression caused decrease of contraction response. But KCl response indicated decrease on diabetic bladder compared with control one. Depolarization contraction didn't involve muscarinic receptor response and was nearly equal total smooth muscle response. It means that smooth muscle contractility was decrease on diabetic bladder. Please discus other possibility of CCh response decreasing on diabetic bladder.

Our response: Thank you for your recommendation. Through your suggestion, we also realized that the CCH responses decrease may be caused by the declined smooth muscle contractility in
model mice, and this conclusion was more precise and rigorous. Therefore, we’ve discussed
other possibility of CCH response decreasing on diabetic bladder as following (Discussion,
page 12, line 6-9).

Moreover, the KCl-induced tension response various from different groups, indicating the
alteration of bladder smooth muscle, which could be another reason contributed to the tension
change of carbachol, CAP and α, β-methylene ATP.

1.4 - STZ induced diabetes followed by destruction of beta cell on islets of pancreas. Why
plasma insulin is increase on author's diabetic model mice? What is mean of STZ
instruction?

Our response: Thank you for your comments. Diabetes can be divided into type 1 and type 2.
Single-high dose STZ intraperitoneal injection directly destroys the islet bate cells of pancreatic,
which is a classical method for establishing type 1 diabetes mellitus model. And the plasma
insulin is markedly decreased in this model mice compared with controls (reference “Camel milk
ameliorates hyperglycaemia and oxidative damage in type-1 diabetic experimental rats” [3]).
However, the type 2 diabetes, characterized by chronic hyperglycemia and high insulin
resistance, is a disease stemming from a combination of cumulative polygenic traits and
interactions with environmental stressors. A diet-induced model can be used to more closely
resemble the gradual progression from obesity to insulin resistance. There were multiple studies
described the development of a type 2 diabetes model by long time high-fat diet feeding and
consecutive multiple low doses of STZ injection. In these studies, there were significant increase
or no markedly change in plasma insulin compared with controls in type 2 diabetic animals, such
as “Anti-diabetic effects of polysaccharides from Talinum triangulare instreptozotocin (STZ)-
induced type 2 diabetic male mice” [4], “Hypoglycemic, hypolipidemic and antioxidant effects
of Sarcandra glabra polysaccharide in type 2 diabetic mice” [5], “Establishment and Assessment
of Mice Models of Type 2 Diabetes Mellitus” [6] and so on. The severe insulin resistance
observed in type 2 diabetes mice would also induce the increase of insulin releasement. In our
study, we established type 2 diabetes mice model by multiple low doses STZ injection and high-
fat diet feeding (more than 20 weeks), resulting in the increase of insulin level.

We are sincerely grateful for editors’ and reviewers’ valuable comments, please feel free to
contact us if further revision on the manuscript is deemed necessary. We look forward to
receiving the outcome of our resubmission of the manuscript in due course

Yours truly

Hongying Cao


