Answering Reviewers

Reviewer #1:

1 One major concern is the lack of in vitro validation to provide a more detailed insights into the mechanism.
Answer: Thanks for your advice. Repeated verification in vivo and in vitro can provide detailed and powerful evidence. However, our study reflects the intestinal GLP-1-neural reflex pathway, which is briefly described below: intestinal: GLP-1→intestinal GLP-1 receptor→vagal afferent fibres→nucleus tractus solitarius→the sympathetic nuclei of the spinal cord→adrenal secretion. This pathway is difficult to study in vitro at present, and may be realized in the future as technology advances. This suggestion provides us with the direction of further experiment.

2 Rigorous proofreading is needed.
Answer: Thanks for your advice. We have conducted a meticulous and thorough proofreading, followed by rigorous scrutiny by native.

3 An abbreviation list should be added. One example, what does “DH” refer to?
Answer: Thanks for your advice. We have finished it.

4 Animal research ethics approval is missing. The cited “SCXK(Lu)20200001” does not seem to be an approval number.
Answer: We check and fill in the corresponding animal research ethics approval number.

5 The manuscript does not have an abstract.
Answer: The abstract section has been supplemented in the original article.

6 Uncropped gels of the western blots should be provided as supplementary
Untrimmed Western blot gels have been provided in the supplementary document.

7 Images in fig 2A are not quite representative of the otherwise clear quantified effects. Replace with more representative images.
Answer: Thanks for your advice. We have selected the representative images and replaced the image in Fig 2A.

8 References should be enriched and updated with more diversified investigations that discuss relevant pathways in greater depth.
Answer: Thanks for your advice. We carefully read the relevant literature provided by the expert, which mentioned the generation of oxidative stress and the mechanism of antioxidants such as vitamin E and hydrogen sulfide in oxidative stress response [PMID: 17151320, PMID: 35517830, PMID: 17151319, PMID: 33255507, PMID: 36432184, PMID: 35740022. PMID: 38440177]. Then we further combined with the retrieval method you provided to search the relationship between hypoglycemia and oxidative stress, and added this relevant content as a supplement in the discussion [PMID: 33123598, PMID: 32179763, PMID: 19303962, PMID: 35453666, PMID: 38426865, PMID: 37591012].

Reviewer #2:
I would like to know if the authors have results on responses to hypoglycemia in the 2 experimental hypoglycemia mouse models regarding the time of day—i.e. nocturnal hypoglycemia. And if yes, to comment it in the Manuscript.
Answer: Thanks for your advice. Unfortunately, we did not pay attention to the nocturnal hypoglycemia in mice. Rodents are different from humans in that they tend to eat more at night, so it is speculated that nocturnal hypoglycemia occurs less frequently in them. However, this is a very
interesting question. We can give them night fasting like humans. Perhaps we will focus on this in future research.
Round 2

Answering Reviewer #2: This reviewer's comments have not been sufficiently addressed.

Answer: Thanks again for the reviewers' comments. We have re-examined reviewers' first comments and suggestions, as well as our revisions to them, and speculate that the reviewers' suggestion this time stems from the first question raised during the first review: “One major concern is the lack of in vitro validation to provide a more detailed insights into the mechanism”. This paper attempted to reveal the intestinal GLP-1-nerve reflex pathway from intestinal GLP-1 to the adrenal medulla, which is interconnected and suitable for in vivo studies. It would be extremely difficult to conduct in vitro studies. So far, through our own efforts and review of relevant literature, we have not found a suitable technology or method to solve this problem. If the reviewers can provide specific guidance or provide relevant literature, we will be very grateful.