

OPEN PEER REVIEW REPORT 1

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Title: The GLP-1/GIP dual receptor agonist DA-CH5 is superior to a single GLP-1 receptor agonist in protecting neurons in the 6-OHDA rat Parkinson Model

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COMMENTS TO AUTHORS

This article examined the differences between Ex-4 and DA-CH5 in the therapeutic effect of PD in vitro and in vivo. On the whole, the authors did comprehensive analysis of the effects of these two drugs on the pathological features of PD, such as the inflammatory cytokines levels, α -syn aggregation, mitochondrial dysfunction, autophagy and apoptosis and insulin resistance. The 2 drugs showed differential and similar effects observed from different readouts of PD, and will be interesting to dissect and discuss why and what are the common and differential mechanisms. Moreover, the comparison between the two drugs in this paper is not detailed enough. The focus was instead more on functions of each the two drugs, that diverted the focus and highlights of this paper. Also, their previous study explored the different effects of dual agonist and single GLP-1 mimetics in MPTP PD model, similar to this paper. will be helpful to describe the differences and links between these two papers. In terms of writing, there are some mistakes or omissions in results and figures, and the format of manuscript will need to be standardized.

Specific comments below:

Page 5, Line 25-31 - These sentences did not state which drug showed good protective effects.

Page 5, Line 42 - 4 dual agonists showed good effects. But in line 52, its stated 2. What happened to the other 2? This is confusing. It is also not clear why eventually the authors focus only on DA-CH5 (page 6, line1).

Page 5, Line 56 - Previous studies to see the dual agonist effect (Feng 2018 and Zhang 2020) are both in MPTP mice, did not refer to 6-OHDA mice.

Page 9, line 39-42 - This sentence needs a reference.

Page 9 and 10, section 2.9 - mice? Should be rat.

Page 14, Line 51 - figure labelling not correct, should be figure 6c

Page 14, Line 52-53 - Should be no difference between Ex-4 and DA-CH5

Page 15, Line 38, duplication of section 3.8, should be 3.9. The following sections need to be relabelled.



Page 22, line 1 - There is no difference in the effect of two drugs on the autophagy related proteins expression in SHSY5Y cells treated by 6-OHDA. The authors should discuss differential and similar effects of the 2 drugs for different assays/readouts.

Discussion/conclusion - authors should discuss on the behavior results. Why are there differences in open-field test but not in rational behavior between the two drugs?