

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Generally, Alzheimer's disease (AD) is the most common neurodegenerative disorder with the current escalation in global aging, and there are no effective drugs to delay progression of the disease. To address this challenge, in this study, the authors aimed at exploring the therapeutic effects of dexmedetomidine (Dex) on AD model mice. The authors used MWM test, Nissl staining, Prussian blue staining, CCK-8 assay, and western blotting to verify their hypothesis. The results showed that Dex can inhibit A β -induced ferroptosis of mouse HNs, and effectively reduce HN loss and cognitive dysfunction in AD mice, both in vitro and in vivo experiments. So, in my opinion, this paper is well-written. The experimental design is reasonable, and the results reflects the conclusion as well. I recommend its acceptance after the minor revision. The detailed comments are:

1) In Table 1, the horizontal and vertical titles should be interchanged to improving the readability for the readers.

Reply: Thank you for your feedback, we have revised the article.

2) Although the author organized the manuscript very well, there are still some typo and grammar errors that should be addressed before publication. For example, in the sentence "Alzheimer's disease (AD) is the most common neurodegenerative disorder, and there is currently no effective drugs to delay progression of the disease", is should be are. And in another sentence "That Dex effectively improved hippocampal neuronal loss, cognitive dysfunction, learning and memory abilities in AD mice by regulating the mTOR-TFR1 signaling pathway to reduce iron death", that should be the.

Reply: Thank you for your feedback, we have checked and revised the grammar errors.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors established in vitro and in vivo Alzheimer's disease (AD) mouse models induced by amyloid β -protein ($A\beta$) and used both models to investigate the neuroprotective roles of dexmedetomidine (Dex) on hippocampal neurons (NHs) during the AD progress, as well as revealed the underlying mechanism. After reasonable setting groups for SPF C57BL/6 mice as Sham, $A\beta$, Dex, and Dex+rapamycin (RAPA) groups, the authors showed that Dex enhanced lipid peroxidation and iron influx in mouse HNs in both in vitro and in vivo experiments, while inhibition of the mTOR axis blocked this process. This result also draws a conclusion that the therapeutic role of Dex on AD is realized via activating mTOR-TFR1 signaling. In short, the topic of this manuscript is timely and interesting. The authors have organized the manuscript rationally, with good methodology and well-written English. However, some important editing needs to be done before publication:

1. In this study, the authors provided comprehensive figures to demonstrate their hypothesis. However, the statistic difference should be showed in the quantitative graphs.

Reply: Thank you for your feedback, we have labeled the statistical symbol using "a, b, c".

2. I noticed that the authors used all male mice in their experiments, is there any particular reason?

Reply: Thank you for your feedback, the physical condition of males is more stable than that of females, and the differences between individuals are smaller. Thus, we used all male mice in the experiments.