

PEER-REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-18-00240

Title: Loss of canonical Wnt signaling is involved in the pathogenesis of Alzheimer's disease

Reviewer's Name: Yun-Bae Kim

Reviewer's country: Korea

Date sent for review: 2018-04-08

Date reviewed: 2018-04-15

Review time: 7 Days

COMMENTS TO AUTHORS

In the review, the authors explained the role of dysfunction of Wnt signaling in the amyloidogenesis, as a possible triggering factor of Alzheimer disease (AD). The review may provide readers with a good information on the pathobiology of AD.

- 1) Although Purro et al. (2012) demonstrated that an increased level of the Wnt/ β -catenin antagonist Dkk-1 is necessary to produce A β -mediated synaptic loss, there is no evidence of relationship with A β peptide accumulation and neurotoxicity (independent of A β peptide?). It is necessary to clarify whether synaptic failure alone related to impaired Wnt/ β -catenin (without A β -mediated synaptic loss) can result in memory deficits.
- 2) Although activation of Wnt/ β -catenin signaling recovers the hippocampus-dependent cognitive impairment, no detailed mechanism(s) were suggested how acetylcholine, a cholinergic neurotransmitter responsible for memory acquisition, can be restored. It there any reports that Wnt/ β -catenin signaling in the cholinergic nervous system plays a role for acetylcholine synthesis via activation of choline acetyltransferase?
- 3) For elimination of accumulated A β , enzymes neprilysin and insulysin from microglia are required. It is recommended that any relationship between Wnt/ β -catenin signaling and A β elimination (via microglial activation?) should be described.

PEER-REVIEW REPORT 2

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-18-00240

Title: Loss of canonical Wnt signaling is involved in the pathogenesis of Alzheimer's disease

Reviewer's Name: Paulina Carriba

Reviewer's country: UK

Date sent for review: 2018- 04-08

Date reviewed: 2018-04-20

Review time: 12 Days

COMMENTS TO AUTHORS

Authors detail in this manuscript the relevance of Wnt signalling in the onset and evolution of Alzheimer's disease (AD).

The article is really interesting and correctly written. Manuscript is organised with a description of how Wnt is involved in the key pathological hallmarks of the disease and then, the authors develop in a large description such involvement in the production of toxic amyloid fragments; tau hyperphosphorylation; and synaptic and memory effects.

After reading the review it is patent that Wnt signalling is a potential target in AD. In that sense, I miss some information about therapeutic clinical approaches. Does the authors know if there is any clinical trial testing the beneficial effects of Wnt activation? Another interesting question is to know if targeting to Wnt could have any adverse/undesirable effect? In my opinion these two aspects should be introduced in the text.