Group #48

Group #48 Elevator Pitch Video Link: https://youtu.be/lsgFB19wcRQ

Alzheimer's: Can astrocytic LRP1 rescue impaired hippocampal neurogenesis in rodents?

Kyuree Kim

Thomas Jefferson High School for Science and Technology, Alexandria, VA, United States

Alzheimer's disease (AD), the most common form of dementia, is an age-related neurodegenerative disease characterized by progressive memory loss[1]. One biomarker of AD is amyloid-beta (Aβ) plaque deposition, which is hypothesized to impair hippocampal neurogenesis[1]. Previous studies revealed that low-density lipoprotein receptor-related protein 1 (LRP1) mediates Aβ metabolism[2–6]. Particularly, LRP1 in astrocytes plays an important role in hippocampal Aβ clearance[6]. Therefore, this study aims to investigate whether increasing astrocytic LRP1 (aLRP1) can rescue impaired adult hippocampal neurogenesis in AD mouse model brains. We will assess adult APP/PS1 mice models with altered aLRP1 levels (upregulated and control). An adenovirus will be used to transfect APP/PS1 mice with either an LRP1 overexpression construct containing an astrocyte-specific promoter (GS) or a control construct. We will then perform immunofluorescence to quantify the number of Aβ plaques (pan-Aβ), mature neurons (NeuN), immature neurons (NeuroD1), and neural precursor cells (Sox2). A BrdU assay will also be conducted to measure the number of proliferating Sox2-positive cells. Additionally, these mice will be assessed for memory retention using behavioral tests such as the Morris Water Maze test. Because aLRP1 has been shown to clear Aβ plaques, we expect that increased aLRP1 levels will be correlated with increased adult hippocampal neurogenesis as well as a better performance on the behavioral tests. These results would provide insight towards the therapeutic benefits of increasing aLRP1 levels to rescue impaired neurogenesis in AD.

Key words: Alzheimer's disease, hippocampal neurogenesis, amyloid-beta, LRP1, astrocytes

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Reference List:

1. Disouky, A. & Lazarov, O. Adult hippocampal neurogenesis in Alzheimer's disease. in *Progress in Molecular Biology and Translational Science* (Elsevier B.V., 2020). doi:10.1016/bs.pmbts.2020.09.002.
2. Kanekiyo, T. & Bu, G. The low-density lipoprotein receptor-related protein 1 and amyloid-β clearance in Alzheimer's disease. *Frontiers in Aging Neuroscience* vol. 6 (2014).
3. Zlokovic, B. v., Deane, R., Sagare, A. P., Bell, R. D. & Winkler, E. A. Low-density lipoprotein receptor-related protein-1: A serial clearance homeostatic mechanism controlling Alzheimer's amyloid β-peptide elimination from the brain. *Journal of Neurochemistry* **115**, 1077–1089 (2010).
4. Kim, J. *et al.* Overexpression of Low-Density Lipoprotein Receptor in the Brain Markedly Inhibits Amyloid Deposition and Increases Extracellular Aβ Clearance. *Neuron* **64**, 632–644 (2009).
5. Kanekiyo, T. *et al.* Neuronal clearance of amyloid-β by endocytic receptor LRP1. *Journal of Neuroscience* **33**, 19276–19283 (2013).
6. Liu, C. C. *et al.* Astrocytic LRP1 mediates brain Aβ clearance and impacts amyloid deposition. *Journal of Neuroscience* **37**, 4023–4031 (2017).