Development of Multi-target therapy for Alzheimer's disease using human neural crest-derived stem cells

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Purpose Stem cell transplantation is a promising therapeutic strategy for the treatment of many neurological disorders. The therapeutic effects, however, are sometimes inconsistent and unpredictable. Human neural crest-derived nasal turbinate stem cells (hNTSCs) are an excellent alternative source of adult stem cells for clinical use because they can be obtained easily by minimally invasive collection procedures and expanded rapidly *ex vivo* for transplantation. Moreover, the characteristics of hNTSCs, including their proliferation, differentiation, and immunophenotype, are not affected by donor age or passage number (Hwang et al., 2013), while other kinds of stem cells exhibit age and passage-related reduction in multiple characteristics. **Method** In the present study, we validated the hypothesis that hNTSCs are a clinically promising therapeutic source of adult stem cells for the treatment of Alzheimer's disease (AD). Here, we evaluated the tprotective effect of hNTSCs against amyloid-β peptide ($A\beta_{1-42}$) neurotoxic activity in culture of human brain organoid (hBO). hNTSCs were evaluated in comparison with human bone marrow-derived mesenchymal stem cells (hBM-MSCs) according to the effect of transplantation on AD pathology, including PET/CT neuroimaging, immune status, and cognition, in a 5×FAD transgenic mouse model of AD. **Results and Discussion** Treatment of hBO with $A\beta_{1-42}$ induced neuronal cell death concomitant with decreased expression of neuronal markers, which was suppressed by hNTSCs cocultured under $A\beta_{1-42}$ exposure (Lim et al., 2022). Transplantation of hNTSCs greatly reduces the levels of Aβ42 and the number of microglia, concomitant with increased survival of hippocampal and cortex neurons when compared with transplantation of hBM-MSCs (Lim et al., 2021). Notably, compared with transplantation of hBM-MSCs, transplantation of hNTSCs significantly enhanced performance on the Morris water maze, with an increased level of TIMP2, which is necessary for spatial memory in young mice and neurons. These results reveal a promising therapeutic effect of hNTSCs and suggest a potential application of hNTSCs of future treatment for patients with AD.

References

Hwang SH, Park SH, Choi J, Lee DC, Oh JH, Yeo UC, Kim SW. Age-related characteristics of multipotent human nasal inferior turbinate-derived mesenchymal stem cells. PLoS One. 2013;8(9):e74330.

Lim JY, Park SI, Park SA, Jeon JH, Jung HY, Yon JM, Jeun SS, Lim HK, Kim SW. Potential application of human neural crest-derived nasal turbinate stem cells for the treatment of neuropathology and impaired cognition in models of Alzheimer's disease. Stem Cell Res. Ther. 2021;12:402.

Lim JY, Lee JE, Park SA, Park SI, Yon JM, Park JA, Jeun SS, Kim SJ, Lee HJ, Kim SW, Yang SH. Protective effect of human neural crest-derived nasal turbinate stem cells against amyloid-β neurotoxicity through inhibition of osteopontin in a human cerebral organoid model of Alzheimer's disease. Cells. 2022;11:1029.

Keywords: Alzheimer's disease, human brain organoid, hNTSCs, cell transplantation, 5 × FAD mice

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Impact of transcranial direct current stimulation on cognitive function, brain functional segregation, and integration in patients with mild cognitive impairment according to amyloid-beta deposition and APOE ε4-allele

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Purpose Anodal transcranial direct current stimulation (anodal-tDCS) is known to improve cognition (Liu, C.S., et al., 2017) and normalize abnormal network configuration during resting-state functional magnetic resonance imaging (fMRI) in patients with mild cognitive impairment (MCI) (Binnewijzend, M.A., et al., 2012). We aimed to evaluate the impact of sequential anodal-tDCS on cognitive functions, functional segregation, and integration parameters in patients with MCI, according to high-risk factors for Alzheimer's disease (AD): amyloid-beta (Aβ) deposition and *APOE* ε4-allele status. **Method** In 32 patients with MCI ([18F] flutemetamol-: n = 10, [18F] flutemetamol+: n = 22; APOE ε4-: n = 13, APOE ε4+: n = 19), we delivered anodal-tDCS (2 mA/day, five times/week, for 2 weeks) over the left dorsolateral prefrontal cortex and assessed the neuropsychological test battery and resting-state fMRI measurements before and after 2 weeks' stimulation. **Results and Discussion** We observed a non-significant impact of an anodal-tDCS on changes in neuropsychological battery scores between MCI patients with and without high-risk factors of AD, Aβ retention and *APOE* ε4-allele. However, there was a significant difference in brain functional segregation and integration parameters between MCI patients with and without AD high-risk factors. We also found a significant effect of tDCS-by-APOE ε4-allele interaction on changes in the functional segregation parameter of the temporal pole. In addition, baseline Aβ deposition significantly associated negatively with change in global functional integrity of hippocampal formation. Anodal-tDCS might help to enhance restorative and compensatory intrinsic functional changes in MCI patients, modulated by the presence of Aβ retention and the *APOE* ε4-allele.

References

Liu, C. S., Rau, A., Gallagher, D., Rajji, T. K., Lanctôt, K. L., & Herrmann, N. (2017). Using transcranial direct current stimulation to treat symptoms in mild cognitive impairment and Alzheimer's disease. Neurodegenerative disease management, 7(5), 317-329.

Binnewijzend, M. A., Schoonheim, M. M., Sanz-Arigita, E., Wink, A. M., van der Flier, W. M., Tolboom, N., ... & Barkhof, F. (2012). Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurobiology of aging, 33(9), 2018-2028.

Keywords: amyloid beta deposition; APOE ε4-allele; mild cognitive impairment; transcranial direct current stimulation

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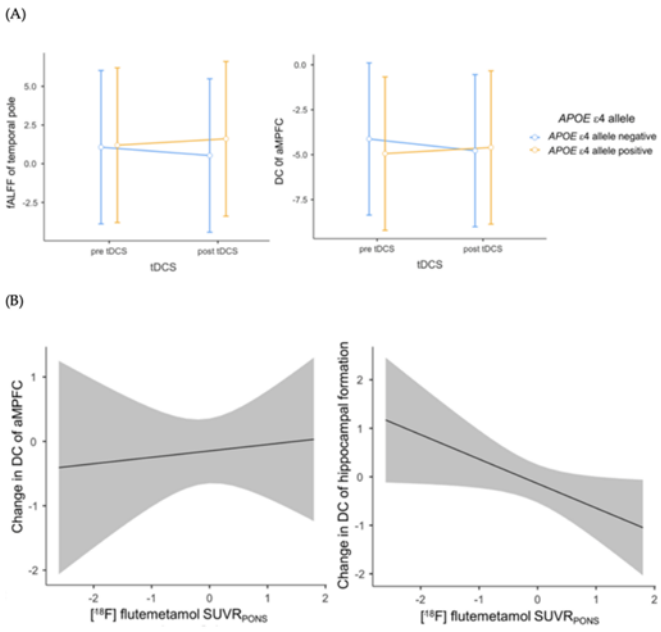
Figure 1. (A) Impact of interaction between tDCS and *APOE* ε4 allele on fALFF and DC. (B) Associations between [18F] flutemetamol $SUVR_{PONS}$ and changes in amplitude of DC



Plasma oligomeric beta-amyloid is associated with cerebral beta-amyloid deposition in cognitively normal older adults

Participants*:* S.-M. Wang, D. W. Kang, Y. H. Um, N.-Y. Kim, H. K. Lim (All from Republic of Korea) **Purpose:** Exploration of Alzheimer's disease (AD) pathology by investigating beta-amyloid, tau, and neurodegeneration are effective in detecting AD at its preclinical phase. However, PET imaging of amyloid, tau, and FDG requires high cost whereas cerebrospinal fluid studies of Aβ42, phosphorylated tau, and total tau are invasive. Beta-amyloid (Aβ) is formed when beta-amyloid precursor protein (APP) is cleaved by beta- and gamma-secretase. Among diverse Aβs, Oligomerized Aβ (OAβ) is known to be the most toxic and is strongly associated with the earlier pathogenesis of AD. Multiple validation studies showed that the Multimer Detection System-Oligomeric Aβ (MDS-OAβ) technique can measure the oligomerization dynamics of Aβ in a plasma sample. We aimed to investigate whether MDS-OAβ can reflect cerebral Aβ deposition in cognitively normal older adults. **Method:** A total of 64 cognitively normal older adults who visited Catholic Brain Healthcare Center, Yeouido St. Mary's Hospital, for medical check-up complaining of cognitive decline were included in the study. Cerebral amyloid statuses were dichotomized into positive or negative based on visual assessment of amyloid positron emission topography (PET) scan (A-PET positive group=40, A-PET negative group=24) using [^{18}F] flutemetamol. All participants received the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K). Plasma OAβ concentration was measured by MDS-OAβ. **Results:** Baseline demographic data of A-PET positive group and A-PET negative group showed no significant difference in gender, age, education, and cognitive function measured using CERAD-K. The plasma MDS-OAβ value was statistically higher in A-PET positive group (0.992 + 0.186) than in A-PET negative group (0.808 + 0.265) ($p<0.01$). Global cerebral Aß retention correlated positively with plasma MDS-OAβ level. Plasma OAβ concentration higher than or equal to 0.90 ng/mL, the cut-off value which was established in a previous validation study, was defined as MDS-OAβ positive. MDS-OAβ positive group (N=38) showed higher cerebral global cerebral Aß retention than MDS-OAβ negative group (N=26), but the difference was not statistically significant ($p = 0.09$). However, when patients having equivocal plasma MDS-OAβ value (0.85 ~ 0.89 ng/mL, N=4) were excluded, the difference of global cerebral Aß retention between two groups became statistically significant ($p<0.05$). **CONCLUSION:** The plasma MDS-OAβ value might reflect cerebral amyloid status and global cerebral Aß retention in cognitively normal older adults. This suggests that the plasma MDS-OAβ test might be considered an adjuvant or alternative to A-PET scan for cognitively normal older adults in clinical settings. However, longitudinal follow-up studies, investigating association between change of plasma MDS-OAβ with that of cerebral Aß retention value, are needed to better understand clinical utility of plasma MDS-OAβ.

References:

Nah EH, Cho S, Park H, Noh D, Hwang I, Cho HI. Reference interval and the role of plasma oligomeric beta amyloid in screening of risk groups for cognitive dysfunction at health checkups. J Clin Lab Anal. 2021 Sep;35(9):e23933. doi: 10.1002/jcla.23933. Epub 2021 Aug 3

Youn YC, Lee BS, Kim GJ, Ryu JS, Lim K, Lee R, Suh J, Park YH, Pyun JM, Ryu N, Kang MJ, Kim HR, Kang S, An SSA, Kim S. Blood Amyloid-β Oligomerization as a Biomarker of Alzheimer's Disease: A Blinded Validation Study. J Alzheimers Dis. 2020;75(2):493-499. doi: 10.3233/JAD-200061.

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