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   2019G028

2. Title
   Attempt to develop a therapeutic method for dementia using human iPS cell-derived neural cell transplantation and nicotinic administration

3. Period
   2019-2021

4. Summary

   There are an increasing number of dementia patients due to the aging of Japanese society. It is expected to develop truly effective treatments for dementia. We investigated whether it is useful as a novel cell therapy for dementia to induce differentiation and transplantation of nerve cells from human iPS cells. We have previously shown in preliminary experiments that the combined use of nicotine administration with neuronal cell transplantation improved cognitive function more effectively using dementia model mice. We here investigated the mechanism. After inducing an embryoid body (EB) from undifferentiated human iPS cells, neural differentiation was induced by stimulation with three factors: retinoic acid, sonic hedgehog, and noggin. These neurons were transplanted into the bilateral hippocampus of PDAPP mice, which are a model of dementia. Cognitive function was assessed by the Morris Water Maze (MWM) test before and after transplantation. Immunohistochemical staining was performed on the brain sections. Especially, we focused on phosphorylated Akt expression of human nicotinic acetylcholine receptor (α7nAChR) expressing neurons. Similarly, after transplantation to old-age PDAPP, nicotine was administered and then an MWM test was performed to evaluate the effect of nicotine administration on improving cognitive function. Significant improvement in cognitive function was observed in transplanted mice. Transplanted neurons engrafted in the host and differentiated into cholinergic nerve and nicotinic acetylcholine receptor (α7nAChR) -expressing cells in the hippocampus and cerebral cortex. The effect of transplantation on aged PDAPP mice was not as good as that of young PDAPP mice, however the combined use of nicotine with neuronal cell transplantation improved cognitive function to the same level as that of young PDAPP mice. In dementia mice with transplantation, α7nAChR-expressing cells were further activated by nicotine administration and expressed phosphorylated Akt in the hippocampus efficiently. In particular, the expression of phosphorylated Akt was remarkable in the hippocampal CA2 region. Neuronal cell transplantation increased a numbers of nACRalpha7 positive neuronal cells, indicating that nicotine activates more efficiently accompanying their phosphorylated Akt expression. There is a need to explore the possibility of further improving cognitive function by combining neuronal transplantation with nicotine administration.