Neural Transplantation

To THE EDITOR: I read with interest the article by Takagi, et al. (Takagi Y, Nishimura M, Morizane A, Takahashi J, Nozaki K, Hayashi J, et al: Survival and differentiation of neural progenitor cells derived from embryonic stem cells and transplanted into ischemic brain. J Neurosurg 103: 304–310, August, 2005), concerning the transplantation of neural progenitor cells (NPCs) derived from embryonic stem cells (ESCs) into the ischemic mouse brain. The authors confirmed previous experiences of other researchers about the survival and differentiation of these cells in the ischemic area.

Abstract

Object. Cell replacement therapy including the use of embryonic stem cells (ESCs) may represent a novel treatment for damage from stroke. In this study, the authors transplanted neural progenitor cells (NPCs) derived from ESCs into ischemic brain and analyzed their survival and differentiation.

Methods. Multipotent NPCs were generated from ESCs by using the stromal cell–derived inducing activity method. These cells could differentiate in vitro into neurons, glia, and oligodendrocytes, thus revealing them to be neural stem cells. The NPCs were then transplanted into ischemic brain. At 2 weeks postischemia, the transplanted cells occupied 18.8 ± 2.5% of the hemispheric area; by 4 weeks postischemia, 26.5 ± 4% of the hemisphere. At 4 weeks after transplantation, green fluorescent protein (GFP)–positive transplanted cells showed mature neuronal morphological features. The authors also investigated the expression of differentiation markers and various neurotransmitters. Transplanted cells were immunopositive for neuronal nuclei, β-tubulin-III, and glial fibrillary acidic protein. Of the GFP–positive cells, 33.3 ± 11.5% were positive for glutamate decarboxylase, 13.3 ± 5.8% for glutamate, 2.1 ± 2.5% for tyrosine hydroxylase, 1.8 ± 2% for serotonin, and 0.4 ± 0.2% for choline acetyltransferase.

Conclusions. The authors confirmed the survival and differentiation of ESC-derived NPCs transplanted into the ischemic brain. Surviving transplanted cells expressed several neural markers and neurotransmitters. These findings indicate that these cells can function in the brain.

I wish to point out that replacement cells (embryonic or fetal grafts, NPCs, and ESCs) used to treat an ischemic brain and/or ischemic penumbra zone must be revascularized with omental tissue, because rapid and efficient revascularization of these grafts is a prerequisite for improving function and prolonging graft survival.7,9

Neurosurgical findings have demonstrated that some challenging diseases8,11,12 such as neurogenic hypertension (the main representative of essential arterial hypertension), Huntington disease (HD), Alzheimer disease (AD), Parkinson disease (PD), and Type 2 diabetes mellitus are primarily caused by progressive hypoperfusion and hypometabolism in the intraparenchymal territory of the Heubner recurrent, anterior choroidal, and perforating arteries as a result of atherosclerotic plaques located at the mouths of these arterial branches. In contrast, the function of neurons and axons in residual nervous tissue in patients with ischemia and ischemic penumbra can improve immediately if blood flow is restored through the omentum, and later because of neuronal regeneration. Neurological improvement is better during the 1st weeks after surgery than in the following months or years. For these reasons, I believe that these diseases can be cured in the earlier stages, because their primary cause is related to vascular anomalies and atherosclerotic plaques located at the supraclinoid carotid arteries (CAs), circle of Willis, and distal end of the basilar artery.

Neural transplantation for the treatment of PD was initiated in March 1987 by Li,14 and for HD by Sramka and colleagues in June 1990.16 Therefore, transplantation of embryonic brain tissue into the septal nuclei13 or of NPCs for the treatment of moderate AD13 is feasible for the following reasons. First, mild AD17 is characterized by impairment of short-term memory (typical course, ~ 70% of cases) or behavioral and personality changes (atypical course, ~ 30% of cases), both as initial symptoms and less frequently (~ 25% of cases) associated with visual, olfactory, and gustatory deficits. Clinical findings suggest that AD is initiated in the mesial temporal lobes and/or subcommissural regions.

Second, the mesial temporal lobe (hippocampal formation, entorhinal region, and amygdaloid body) receives all of the exteroceptive (sensory afferent input) and interoceptive (autonomic afferent input) stimuli.17,18 For this reason, especially the hippocampal formation (dentate gyrus, Ammon horn, and subicular complex) is associated with learning and short-term memory;17,20 through efferent projections, it is associated with emotional behavior, motor response, and endocrine and autonomic functions, among other actions.

Third, the subcommissural region (also known as the substantia innominata or basalis of Meynert) is constituted by cholinergic and neuropeptidic nuclei, as well as their fiber bundles, especially the medial forebrain bundles.8,11,15 From here, the cell bodies of cholinergic neurons send long axons through 1) the external capsule to finish as axonic terminals in the cerebral cortex of the lateral surface of the cerebrum; 2) the fornix to finish in the mesial temporal lobe, especially in the hippocampal formation; 3) the cingulate bundles to terminate in the cerebral cortex of the medial surface of the cerebrum; 4) the olfactory tracts and bulbs; and 5) to diencephalic structures. Thus, acetylcholine synthesized by the cholinergic neurons is transported by the axons, and the neurotransmitter is released by the axonic terminals within the synaptic cleft. In other words, the cell bodies and dendrites of these cholinergic neurons located in the subcommissural region have a key role in the functioning of the neocortex and limbic lobes. Malfunction in this region and its orbitofrontal projections are involved in the pathogenesis of schizophrenia, affective and psychotic symptoms, short-
Clinical data suggest that AD has a microvascular origin in the intraparenchymal territory of the anterior choroidal and anterior perforating arteries.

Fifth, we recently (August 20, 2005) transplanted omental tissue onto the optic chiasm, CA bifurcation, and anterior perforated space (APS) in a 74-year-old man with moderate AD (typical course) for 4 years. During surgery, we made three important observations: 1) severe atherosclerosis of the left supraclinoid CA and its terminal branches; 2) approximately six exsanguinated anterior perforating arteries; and 3) some perforating branches with residual blood flow centripetal to the origin of the vessels (unpublished observations). This patient experienced neurological improvement beginning on the 3rd postoperative day, and at present he shows evidence of objective improvement in the symptoms of AD, although impairment in short-term memory persists without cholinesterase inhibitors.

Therefore, based on these anatomical, clinical, and neurosurgical findings in patients with AD, my colleagues and I propose two surgical procedures to treat this disease: 1) omental transplantation onto the optic chiasm, CA bifurcation, and APS in patients with mild AD; and 2) combined NPC and omental transplantation in patients with moderate-stage AD (that is, implantation of NPCs producing acetylcholine and neuropeptides in the subcommissural region and/or mesial temporal lobe).

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References

RESPONSE: Dr. Rafael reports on the role of the omental graft in cell replacement therapy and the potential use of omental grafting as a novel treatment for AD. The methods of revascularization against ischemic brain tissue have been discussed widely. Angiogenic factors including basic fibroblast growth factor, vascular endothelial growth factor and so forth, have been delivered by various methods into ischemic tissue in animals. Regarding the omental graft, Yonkawa and Yaşargil first used omental transplantation for the treatment of cerebral ischemia in 1977. More recently, Goldsmith reported on the successful omental graft treatment of patients with AD. In that report, Goldsmith posited that omentum may increase cerebral blood flow (CBF) and have angiogenic, neurotransmitting, and nerve growth substances in its tissues. It is theorized that these biological factors favorably affect still viable but deteriorating ischemic-sensitive neurons located within the brain affected by AD. Considered as a means for increasing CBF, bone marrow–derived endothelial progenitor cells have been effectively used in experimental models. In the near future, endothelial progenitor cell transplantation may substitute for the omental graft. As for neuronal stem cell transplantation, several sources are possible including neural stem cells, bone marrow, and embryonic stem cells (ESCs). My colleagues and I have shown that monkey ESC–derived neural stem cells improve the symptoms of experimentally induced PD. In addition, we proved that mouse ESC–derived neuronal stem cells survive and differentiate in ischemic brain tissue and that monkey ESCs showed network formation with host neurons. Although many problems (including ethical ones) exist, ESCs have potential as a neuronal transplantation therapy for the ischemic brain.

In summary, I agree with Dr. Rafael’s opinions. An ischemic zone should be revascularized by some method before the patient undergoes neuronal transplantation.

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References
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