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Research Report

Embryonic neural stem cells transplanted in middle cerebral artery occlusion model of rats demonstrated potent therapeutic effects, compared to adult neural stem cells

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ABSTRACT

Cell therapy using stem cells is awaited by stroke patients with impaired movement and cognitive functions, although intravenous alteplase-administration ameliorated outcomes of patients receiving the therapy within 3 h of onset. In this study, we explored the therapeutic effects of neural progenitor cells (NPC) upon middle cerebral artery occlusion (MCAO) model of rats with exploration of the differences between adult and embryonic NPCs in therapeutic effects. GFP-labeled adult or embryonic NPCs were transplanted for transient MCAO model of rats at 1h after reperfusion. Rats were examined behaviorally using limb placement test, rotarod test and cylinder test with neuroradiological assessment using magnetic resonance imaging (MRI). Consequently after euthanasia, rats were immunohistochemically investigated to explore graft survival and immune reaction. MRI of rats receiving NPCs revealed significant reduction of infarct volumes, compared to vehicle-treated rats with corresponding behavioral amelioration. The transplanted cells were surviving in rats receiving NPCs, although the number of embryonic NPCs was significantly higher than that of adult NPCs. Iba-1-positive inflammatory cells of rats receiving adult NPCs were prominent, compared to those receiving embryonic NPCs, which might be a rationale for the differences between rats receiving adult and embryonic NPCs in the number of surviving NPCs. On the contraries, adult NPCs surely demonstrated therapeutic effects with a few surviving cells, thus indicating that the therapeutic effects might be due to trophic/growth factor-secretion from transplanted NPCs, rather than replacement of damaged host neurons. Therapeutic effects of NPCs for MCAO model of rats were clarified in this study. Transplantation of NPCs

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Abbreviations: BBB, blood–brain barrier; BDNF, brain–derived neurotrophic factor; BrdU, bromodeoxyuridine; CNPase, 2′, 3′-cyclic nucleotide 3′-phosphodiesterase; CNS, central nervous system; DAPI, 4′, 6-diamidino-2-phenylindole dilactate; Dcx, doublecortin; EGF, epidermal growth factor; FGF, fibroblast growth factor; GDNF, glial cell-line-derived factor; GFAP, glial fibrillary acidic protein; LPT, limb placement test; MCAO, middle cerebral artery occlusion; MSC, mesenchymal stem cell; NGF, nerve growth factor; NPC, neural progenitor cells; SCF, stem cell factor; SVZ, subventricular zone; T2WI, T2-weighted images

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will be a hopeful strategy for stroke patients, although further studies are required for the patient safety and underlying mechanisms.

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1. Introduction

Intravenous administration of alteplase is safe and effective for cerebral infarct when it is used within 3 h of onset (Wahlgren et al., 2007). However, the therapeutic time window is narrow and other therapeutic strategies are awaited especially by stroke patients in subacute and chronic stages. Originally, transplantation therapy was established for the organs with highly proliferative potentials, such as liver transplantation for liver cirrhosis and skin transplantation for burning. Recently, regenerative therapy to the central nervous system (CNS) has reached the level of clinical application by the established methods of isolation and culture of neural stem/progenitor cells. Especially, the cell therapy using neural progenitor cells (NPCs) for stroke to achieve the functional restoration of the damaged neurons might be promising. Stem cells can self-renew and differentiate into multiple lineages suitable for the microenvironment (Akiyama et al., 2001). Furthermore, NPCs might migrate into the damaged area as if it would replace the damaged area

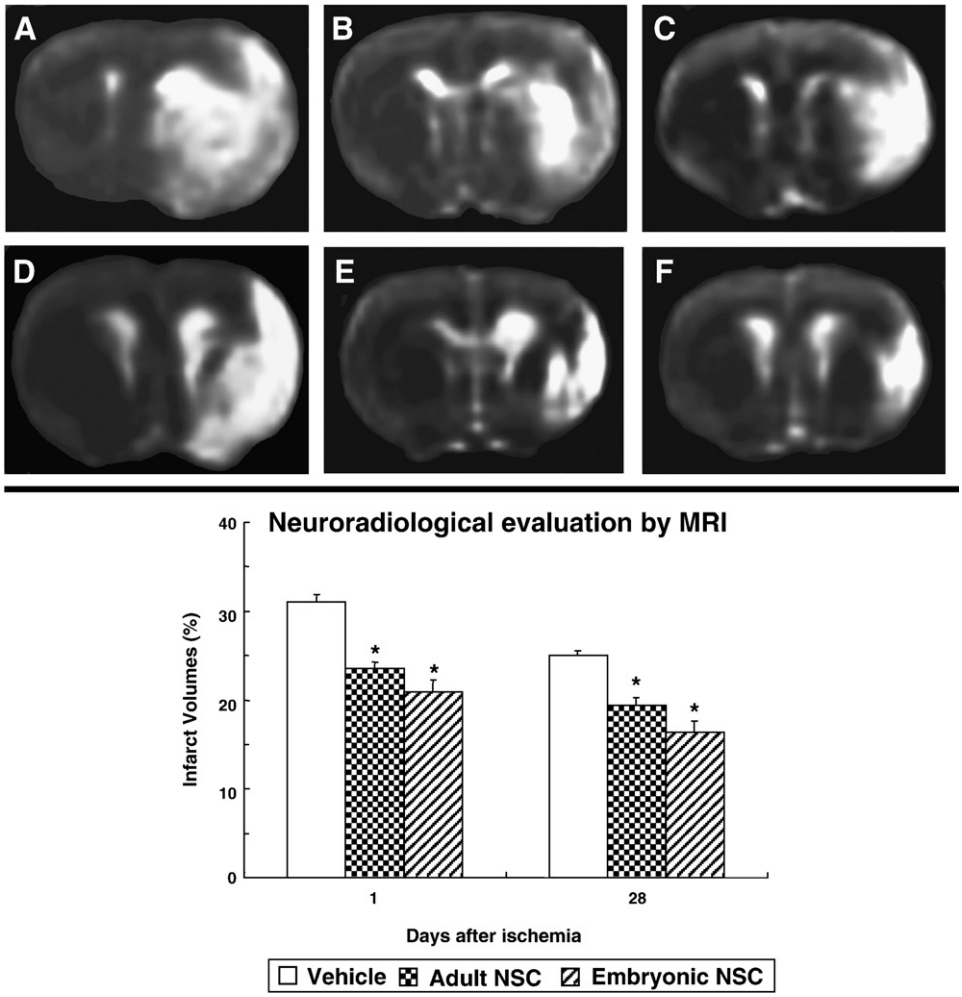

Fig. 1 – Reduced infarct volumes of rats receiving NPCs. Upper column: Representative magnetic T2-weighted images (T2WI) obtained at 1 and 28 days after administration of NPCs or vehicle (vehicle: A and D, adult NPC: B and E, embryonic NPC: C and F) demonstrate that large high-intensity area at 1 day after MCAO reduces at 28 days in all rats. Furthermore, the high-intensity area of rats receiving NPCs is smaller than that of rats in the vehicle group. Lower column: The graph displays that high-intensity area of rats receiving adult or embryonic NPCs is significantly smaller than that of rats in the vehicle group both at 1 and 28 days after transplantation. The effects to reduce infarct volumes of rats receiving embryonic NPCs tend to be more prominent, compared to those of rats receiving adult NPCs, in spite of no significant differences. Data are expressed as mean percentages of infarct volumes ± S.E., relative to the volume of intact hemisphere. ($n = 8$ each, $^{*}p < 0.05$ vs. vehicle group).

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