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Rapid communication

Beneficial effect of pharmacological mobilization of bone marrow in experimental cerebral ischemia

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Abstract

Bone marrow stem cells are able to differentiate into nervous and endothelial cells. In our study, we found that administration of a bone marrow-stimulating factor (granulocyte colony-stimulating factor; G-CSF 50 μg/kg) decrease the brain infarct volume and enhance survival rate in a model of cerebral ischemia. Taken together, these data suggest a beneficial effect of a pharmacological endogenous bone marrow mobilization in the course of cerebral ischemia and open a new direction for cellular therapy strategy in stroke.

Keywords: Cerebral ischemia; Growth factor; Bone marrow

Bone marrow stem cells are able to differentiate into neuronal cell (Mezey et al., 2000) and endothelial cell (Hess et al., 2002). These properties explain that exogenous administration of bone marrow can experimentally repair brain in some pathological circumstances with cerebral lesion (Brazelton et al., 2000). Heterologous administration of bone marrow cells induces a decrease in infarct volume by differentiation of bone marrow cells into both neurons and glial cells (Li et al., 2001). Bone marrow injection in cerebral ischemia has permit to develop new strategies in a pathology, in which pharmacological approaches for neuroprotection remain elusive (Chen et al., 2001).

In addition, brain has self-repair capacity by endogenous neurogenesis resulting from differentiation of neuronal stem cell localized into dentate gyrus, hippocampus or subventricular area. We have studied whether pharmacological endogenous mobilization bone marrow by a growth factor (granulocyte colony-stimulating factor; G-CSF) induces a neuroprotection in the course of cerebral ischemia.

The protocol complies with the European Community guidelines for the use of experimental animals. Cerebral ischemia was induced by a technical procedure adapted from rat (Puisieux et al., 2000). Male C57/BL6 mice (IFFA Credo, France) were anesthetized with chloral hydrate (300 mg/kg intraperitoneally) and subjected to a 60-min intraluminal middle cerebral artery occlusion with a nylon monofilament suture (6.0), which was removed at the end of occlusion to allow reperfusion.

Mice received, 24 h after intraluminal middle cerebral artery occlusion, a subcutaneous injection (0.1 ml) of G-CSF (50 μg/kg; $n=12$) or its vehicle (saline 0.9%; $n=15$). Surviving mice were sacrificed 4 days after intraluminal middle cerebral artery occlusion and the brains were removed and frozen. Cryostat-cut coronal brain were stained with cresyl violet and infarct volume was assessed as previously described (Bordet et al., 2000).

Data expressed as means ± S.E.M. were analyzed for statistical significance ($P<0.05$) by one-way variance and post hoc protected least significant difference (PLSD) Fisher test or by chi-square test for survival analysis.

Fig. 1A shows that in G-CSF-treated mice, survival rate (75%) was significantly increased 4 days after intraluminal middle cerebral artery occlusion as compared to vehicle-treated mice (20%). Moreover, infarct volume measured in surviving mice was significantly ($P<0.02$) lower in G-CSF-treated mice (27 ± 7 mm^3; $n=9$) than in vehicle-treated mice (69 ± 5 mm^3; $n=3$) (Fig. 1B).

This study demonstrates for the first time, the beneficial effect of a pharmacological endogenous bone marrow mobilization in the course of cerebral ischemia. In addition to exogenous administration of bone marrow, endogenous

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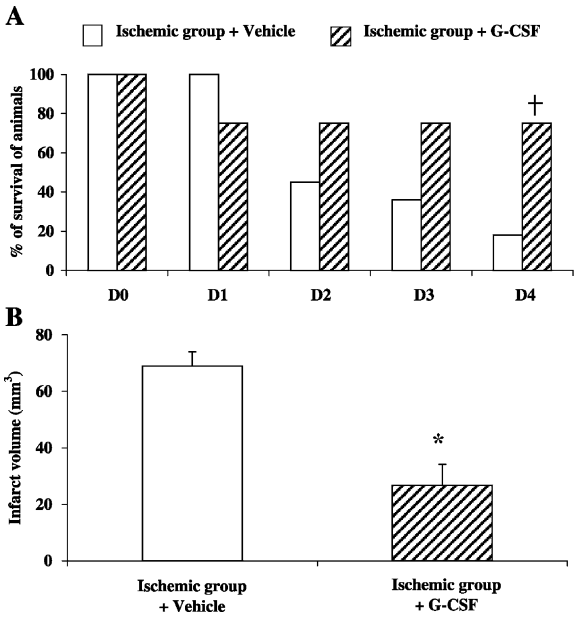

Fig. 1. (A) Survival analysis during the 4 days after intraluminal middle cerebral artery occlusion in mice receiving G-CSF (50 μg/kg in one injection 24 h after the end of occlusion) or its vehicle. †$P<0.01$ as comparison between G-CSF and vehicle at each time. (B) Effect of G-CSF on infarct volume size 4 days after intraluminal middle cerebral artery occlusion in surviving mice. *$P=0.02$ as compared to vehicle-treated mice.

bone marrow could be a source of cells to brain repair. The beneficial effect of a pharmacological endogenous bone marrow mobilization, described also in another ischemia model (Orlic et al., 2001), suggests the interest of this new strategy.

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