Effects of administration routes on migration and distribution of neural progenitor cells transplanted into rats with ischemia

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Background and Purpose: Transplantation of neural progenitor cells (NPCs) following experimental stroke has been shown to improve functional recovery[1]. Therapeutic benefit depends on migration and localization of grafted cells within the target tissue, which can be dynamically detected with MRI[1]. However, it is not clear how the route of cell administration affects this process. We investigated the effects of intra-arterial (IA), intracisternal (IC) and intravenous (IV) injection on migration and distribution of transplanted NPCs in the rat parenchyma using MRI.

Materials and Methods: Male Wistar rats (300-350 g, n = 38) were subjected to 2-hour intraluminal temporary middle cerebral artery occlusion (MCAo), followed 1 day later by administration of NPCs labeled with superparamagnetic iron oxide (SPIO)[2]. Rats with transient MCAo were randomly assigned to one of three treatment groups targeted for cell transplantation intra-arterially (IA, carotid artery, n = 17), intracisternally (IC, cisterna magna, n = 9) or intravenously (IV, tail vein, n = 12). Approximately 1 x 10^6 cells for IA and IV and 1 x 10^5 cells for IC were slowly injected over a 5-minute period. No immunosuppressants were used. *In vivo* MRI measurements consisting of T2-weighted imaging and 3D gradient echo imaging were performed 24 hours post-MCAo (before cell injection), 4h after injection, and once a day for 4 days (**Fig. 1**). All rats were killed 4 days after cell transplantation. Prussian blue (PB) staining was used to identify the labeled cells in the host brain histologically, 3D MRI to detect cell migration and distribution *in vivo*, and T2 map to assess volume of ischemic lesions.

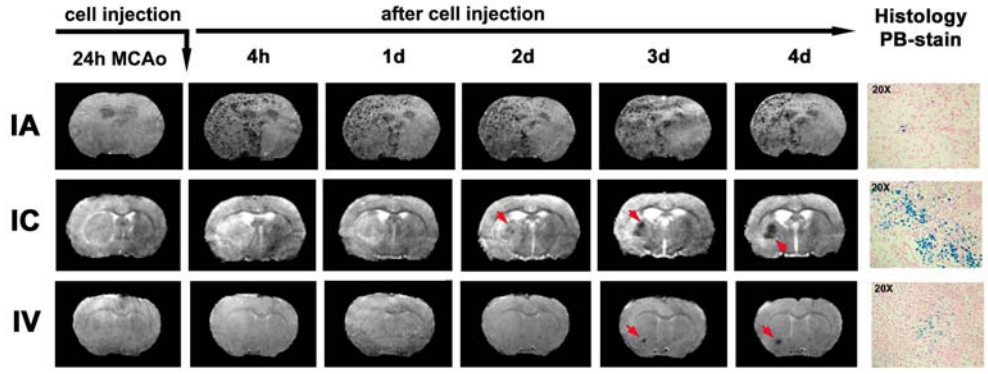

Fig. 1 Consecutive 3D images of representative animals, showing the migration and distribution of iron-labeled NPCs in the host brain after IA, IC and IV cell transplantation following transient MCAo.

Results: When we compared PB-stained tissue sections with the corresponding MRI images, the histological location of the PB-positive cells (iron) coincided with the dark site seen on 3D MRI. With all three delivery routes, both histological evaluation and MR imaging showed that most of these transplanted cells were located on the ischemic side, with very few on the contralateral side. On the ischemic side, cells were located in the lesion core and boundary regions, including the cortex, striatum and lateral ventricle. While the labeled cells could be detected as soon as 4 hours after IA injection, they were not seen until 1 to 2 days after IC or 2 to 3 days after IV injection (**Fig. 1**). IA delivery resulted in earlier appearance, more uniform distribution and larger numbers of transplanted cells in the host brain than IC or IV delivery (**Fig. 1**). However, 41% of animals died with IA, compared to 22% with IC and only 8% with IV administration. Stroke severity on the day of cell transplantation, such as ischemic lesion volume, seemed to be another important factor that mediated cell migration. Using 0.12 mm^3 (20 pixels) of SPIO-induced signal reduction on 3D MRI 4 days post-injection as a threshold to divide animals into groups with fewer or more cells, we found that in each treatment group (IA, IC or IV), a smaller lesion volume on the day of cell transplantation corresponded to fewer cells detected in the brain 4 days after transplantation (**Fig. 2a**). Rats with fewer cells in the brain had a significantly smaller lesion volume on the day of cell transplantation than rats with more cells for all animals studied (**Fig 2b**). However, the amount of cells in the brain did not significantly affect lesion reduction, at least during the short observation time (4 days) (**Fig 2c** & **2d**).

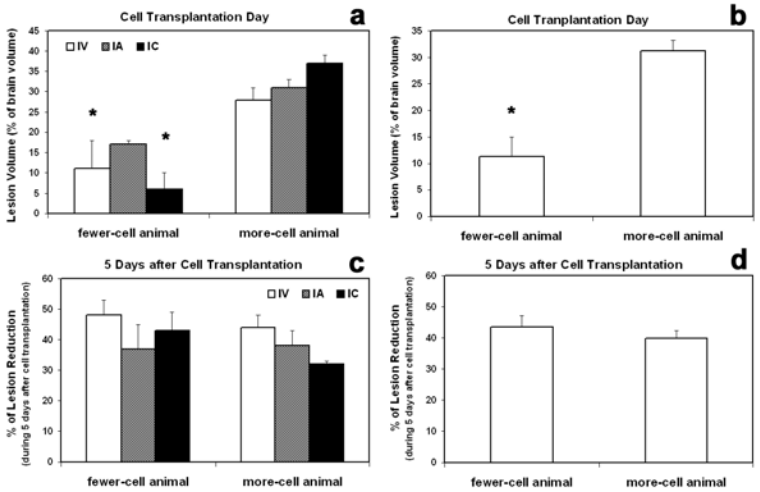

Fig. 2 Lesion volume (**a** & **b**) on the day of cell transplantation and lesion reduction (**c** & **d**) during 4 days after transplantation. **a** & **c**: different treatment groups; **b** & **d**: all animals. *: $p < 0.05$, compare fewer-cell with more-cell animals.

Conclusion: MRI can visualize differences in migration and distribution of magnetically labeled NPCs transplanted into the host brain *via* IA, IC, and IV administration. IA administration following transient MCAo shows advantage in cell migration, distribution and density in the target brain over IC or IV administration. However, high mortality with IA delivery poses a serious issue for protocol optimization. Animals with smaller lesions (less than 10% of brain volume) on the T2 map may get fewer transplanted cells into the parenchyma.

References:

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2. Arbab AS, Yocun GT, Kalish H, et al (2004). Efficient magnetic cell labeling with protamine sulfate complexed to ferumoxides for cellular MRI. Blood. 104:1217-23.