

In-vivo MRI of cell migration towards QA induced lesions in the mouse brain

P. Parasoglou¹, J. J. Rodriguez¹, C. A. Berrios-Otero¹, B. J. Nieman², and D. H. Turnbull¹

¹Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York, New York, United States, ²Mouse Imaging Centre, The Hospital for Sick Children, Toronto, Ontario, Canada

Introduction

It is well established that neural progenitor cells (NPCs) generate neurons throughout life in the subventricular zone (SVZ) of the mammalian brain [1]. These multi-potent neuroblasts (NBs) can travel long distances to the olfactory bulb (OB) along the rostral migratory stream (RMS). Once they reach the bulb, NBs replace olfactory neurons suggesting their potential use for novel cell replacement therapies [2]. Several non-MRI studies have shown that cells from the SVZ also respond to brain injury by migrating towards lesions in the rodent brain [3]. In this work we report the use of MRI to follow simultaneously the movement of magnetically labeled SVZ cells along the RMS [4,5] and towards a quinolinic acid (QA) lesion along blood vessels. The ability to directly monitor cell migration in the mouse brain will enable important investigations of neural cell response to injury.

Methods

In-situ labeling of the NBs in the SVZ with the injection of 50 nL of micron-sized particles of iron-oxide (MPIO) (green fluorescent, 1.63 μ m, Bangs Laboratories) were performed in 6-8 week old female ICR mice (stereotaxic coordinates: 0.8mm lateral, 1.2mm dorsal to bregma and 2.5 mm deep below the pial surface). All MRI experiments were performed using a Bruker Biospec 7.0T system with actively shielded gradient coils (BGA-9S) and a custom quadrature transmit/receive birdcage volume coil (20 mm ID). Mice were screened 48 hours after MPIO injection using a multi-slice FLASH sequence to decide whether NBs in the SVZ were successfully labeled (data not shown). Mice that showed magnetically labeled cell migration to the RMS were injected with 50 nl of 250mM QA (stereotaxic coordinates: 1.2mm lateral, 1.8mm dorsal to bregma and 3.0 mm deep). This QA protocol has been shown previously to induce excitotoxic lesions in the rodent brain. The same mice were imaged 48 h after QA injection. Qualitative estimations of the extent of the QA lesions were identified 48 h post injection, with the use of a multi-slice RARE sequence. A full 3D scan of the entire brain of the brain was used for the visualization of the MPIO distribution; multiple gradient-echo image acquisition was employed (TR = 40, TE = 4.0, 8.3 ms, 12° excitation angle and 9 repetitions). Image dimensions were 256x156x100 with a field of view (FOV) of 25.6x15.6x10.0 mm to yield 100 μ m isotropic voxels in an imaging time of 1h 30 min. Following imaging, mouse brains were perfused with paraformaldehyde and frozen for sectioning and histological analysis.

Results

Hyper-intense pixels in T2-weighted RARE images showed the extent of the QA lesion induced in the mouse brain 48 h post QA injection (Fig. 1A). Magnetically labelled cells from the SVZ migrating to the OB through the RMS are shown in Fig.1B. A second stream of migrating cells is observed in Fig.1C and E from the SVZ, directly towards the site of the QA injection. Histological sections confirmed the presence of fluorescent iron-oxide particles in both sites as shown in Fig. 1D. Immunohistochemical staining showed that the MPIO-labeled cells were following a perivascular route towards the lesions, which was never observed in the images acquired before injection of QA.

Conclusion and discussion

In this study we have showed that MRI can be used to track the movement of magnetically labeled cells from the SVZ towards a QA induced lesion along a perivascular route. Future studies will be focused on identifying the molecular identity of the labeled SVZ cells, using immuno-histochemistry. Additional longitudinal imaging studies will also be performed to establish the timing of neural cell migration into regions of brain injury.

Acknowledgements

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References

- [1] Bayer SA, Nat Med **8**: 963-70, 2006
- [2] Lois C, Science **264**: 1145-48, 1994
- [3] Gordon R, Neuroscience **146**: 1704-18, 2007
- [4] Shapiro EM, Neuroimage **32**: 1150-57, 2006
- [5] Nieman BJ, Neuroimage **50**: 456-64, 2010

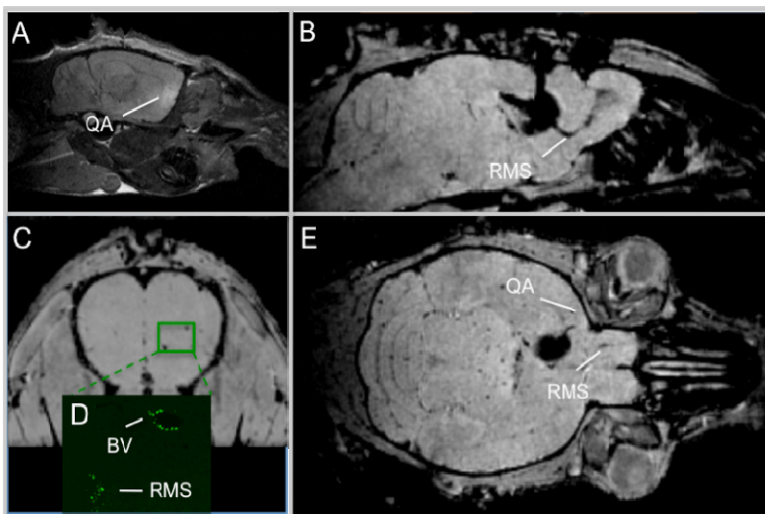


fig.1. A) Sagittal slice, hyper-intense voxels in the area of the QA lesion identified with a T₂ weighted multi-slice RARE sequence. B) Sagittal slice from a 3D gradient echo image, where the NBs migration through the RMS is shown. C) Coronal slice from the same 3D image showing two sites with iron oxide particles. D) Histological confirmation of the existence of fluorescent iron-oxide particles in the RMS and along the blood vessels towards the QA lesion (BV). E) Axial slice from the same 3D image showing the migration of SVZ labeled cells towards the QA lesion and the RMS.