A quantitative comparison of unilateral versus bilateral neural stem cell transplantation in the 3-nitroproprionic acid model of Huntington's disease by contrast agent-enhanced MRI.

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Introduction

Systemic administration of 3-nitropropionic acid (3-NPA) in the Lewis rat produces a selective bilateral striatal GABAergic output neuron degeneration akin to the neuropathology observed in Huntington's disease (HD). This selective loss of neurons in the striatum suggests that cell replacement therapy by means of neural stem cells (NSCs) could provide a potential therapeutic remedy to HD. In order to identify the presence of these cells by MRI and compare their migration or response to damage, it is necessary to pre-label cells for transplantation with an MR contrast agent. The surgical procedure involved in transplantation unfortunately can cause some trauma to healthy brain tissue. It is therefore paramount that as little as possible trauma is caused by the procedure itself, without minimising the potential therapeutic effects of neural stem cell transplantation. Implantation of stem cells into one hemisphere, rather than the two damaged hemispheres, could reduce the risk of iatrogenic damage. The extensive migration of neural stem cells to sites of damage could therefore allow us to transplant cells unilaterally in a bilateral lesion and take advantage of the migratory properties of these cells to colonise all areas of damage. The present study therefore compares quantitatively the temporal and spatial evolution of unilateral and bilateral transplantation of neural stem cells in rats with bilateral damage to the striatum following the injection of the 3-NPA toxin.

Methods

3-NPA Lesion & Transplantation: Striatal lesions were induced in 12-week-old male Lewis rats by administration of 3-NPA (42mg/kg i.p, for 5 days). A 2-week recovery period was allowed prior to commencement of stem cell grafting and serial structural MRI. MHP36 stem cells were labelled with the contrast agent **G**adolinium **R**hodam**I**ne **D**extran (GRID), for 16 hours in proliferative (33^{o}C) conditions prior to transplantation. Grafting consisted of two deposits of 2µl ($5x10^3$ cells) implanted into the striatum and cortex totalling 10^6 cells per hemisphere. Both hemispheres were grafted for bilateral transplants, whilst only the left hemisphere was grafted for unilateral transplants. ***MRI:*** At pregraft (day –2) and postgraft days 2, 7, 14 and 28 days, rats were scanned on a small horizontal bore 4.7 Tesla Varian MRI scanner (Oxford System, UK) to provide T_1-weigthed (TR=855ms, TE=20ms) and a spin echo multi echo (SEME, TR=3000, TE_1=23, TE_2=46, TE_3=69) images. This protocol afforded an acquisition of images with an in-plane resolution of 248µm.

Results & Discussion

The loading of stem cells with GRID provides a means to track survival, migration and integration of transplanted cells in the living 3NPA damaged brain by neuroimaging. Grafts show a dynamic spatial and temporal evolution over time with dispersion away from the injection sites and into the lesion clearly evident by 7 days postgrafting (Fig. 1). Volumetric analysis shows a progressive increase in total graft volume over time in both transplant groups, with the bilateral group showing a volume twice as large as that of the unilateral group (Fig 2A). The increase in graft volume is comparable in each hemisphere in subjects transplanted bilaterally (Fig 2B). However, rats with unilateral transplants showed a larger graft volume in the left hemisphere in comparison to the right 'non-grafted' hemisphere (Fig 2C). GRID-loaded stem cells are present in the right hemisphere as early as 2 days after grafting and graft volume increased over time to reach a comparable size to the left hemisphere by 28 days postgrafting.

Conclusion

This study demonstrates that it is possible to follow the migration and survival of transplanted stem cells quantitatively over time allowing us to compare graft evolution after unilateral and bilateral transplantation. It can be suggested from these results that unilateral transplantation might provide a means to deliver cells to both hemispheres by causing less trauma to the host brain. However, it remains to be investigated if the amount of cells delivered unilaterally will also be sufficient to provide behavioural recovery.

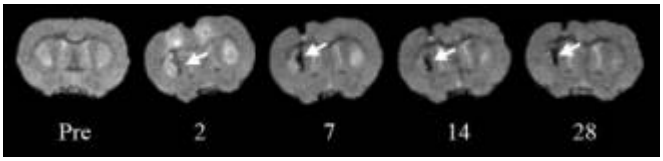

Fig. 1. Shows the evolution of a GRID-labelled unilateral graft developing over time. As time progresses, the graft expands in volume and infiltrates the lesion, whilst in unilaterally grafted animals some cells migrate along the corpus callosum to the non-transplanted, but damaged, hemisphere.

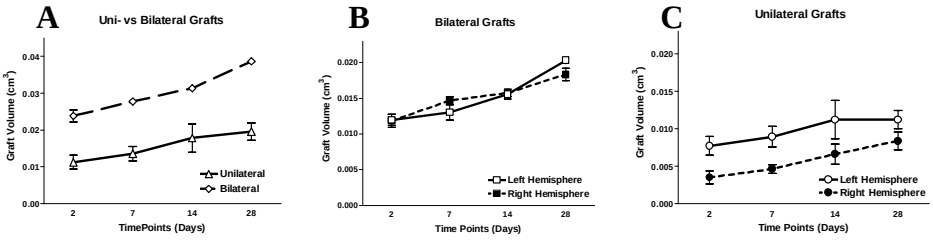

Fig. 2. Shows a quantitative comparison of graft evolution for uni- and bilateral transplants (A) and how grafts in the left and right hemisphere (B&C).