A serial MRI and behavioral assessment of neural stem cell therapy in the 3-nitroproprionic acid model of Huntington's disease.

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Introduction

Cell replacement therapy for neurodegeneration in Huntington's disease (HD) is an attractive novel therapeutic intervention. In order to determine the behavioural effects and underlying neurological correlates associated with stem cell therapy, it is paramount to evaluate how behavioural dysfunctions resolve or improve over time. To model the neurodegeneration observed in Huntington's disease, systemic administration of 3-nitroproprionic acid (3-NPA) causes a selective degeneration of GABAergic output neurons in the striatum of adult rats reflecting many of the pathological signs of HD. To chart the behavioural and anatomical effects of neural stem cell therapy, 3-NPA-lesioned animals were followed serially by a battery of behavioural tests and a comprehensive assessment of structural MRI to probe a suspected relationship between behavioural improvements and neurological correlates.

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). Two weeks post-lesioning, $2x10^5$ MHP36 cells pre-labelled with PKH26 were implanted into each hemisphere (total $4x10^5$ cells per brain). Lesion 'control' animals received sham (*N*-acetyl-cysteine, NAC) injections of the same volume than MHP36-grafted animals to control for possible effects of transplant surgery. ***Behaviour***: Rats were assessed on the beam walk test to determine the progress of motor impairment and 14 weeks following transplantation were also tested on the water maze to probe the animal's cognitive deficits. ***Serial MRI:*** At –3, 0, 2, 4, 8 and 14 weeks following transplantation, rats were scanned on a small horizontal bore 4.7 Tesla Varian MRI scanner (Oxford System, UK). A 3-echo spin echo image was acquired (TR=3.5s, TE_1=0.022s, TE_2=0.044s, TE_3=0.066s, slice thickness=0.7mm and an in plane resolution of 312x312μm).

Results & Discussion

On the beam walk test, sham-grafted animals developed a significant impairment in their motor performance over time. In contrast, animals which received MHP36 stem cell transplants did not significantly differ from control animals suggesting that grafts exerted a beneficial effect on the development of motor degeneration (Fig 1A). At the final time point (14 weeks after grafting) stem cell grafted animals also exhibited a 'partial recovery' on the water maze with both sham-grafted and control animals significantly differing, but MHP36 transplanted animals performing non-significantly different from either group (Fig 1B). Serial MRI assessment also allowed us to assess the progressive neuropathology and possible remedial 'anatomical' effects of the MHP36 cells. However, MHP36 cells did not significantly reduce the size of the lesion relative to baseline (pre-graft) measures compared to animals receiving sham transplants (Fig 2A). Still, a beneficial effect of neural stem cells was observed on the amount of tissue preserved in the striatum suggesting that the effects of MHP36 stem cells might not reverse existing neuropathology, but might prevent further degeneration of 'at risk' tissue (Fig 2B).

Conclusion

Our results suggest that neural stem cells might not revert existing pathology, but can rescue tissue at risk of neurodegeneration. This study shows that MRI can provide important insights into how neural stem cells exert their beneficial behavioural effects and therefore could provide important surrogate markers of graft efficacy

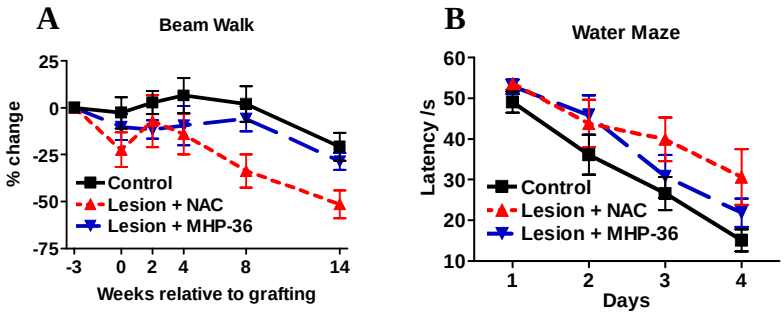

Fig 1. shows that MHP36 transplants prevent the development of a motor impairment that can be observed on the beam walk test (A). Animals with MHP36 transplants also showed some improvement on the water maze, but did not improve to reach the normal control performance (B).

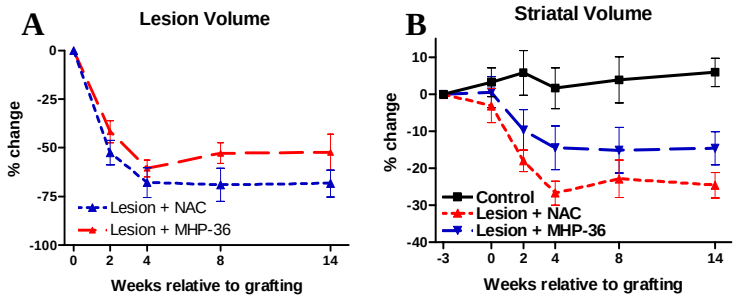

Fig 2. shows the lesion volume that was derived from serial T2-weighted MR images indicating that transplants did not reduce the lesion significantly compared to lesioned animals which received a sham (NAC) transplant (A). However, there was significant sparing of striatal tissue in the transplant group suggesting that MHP36 transplants averted further striatal degeneration (B).