Detection of Transplanted Embryonic Stem Cells in a Parkinson Rat Model by High-Resolution MR-Imaging

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Introduction

Stem cell transplantation is a promising approach for the therapy of Parkinson´s disease (PD) and other neurological disorders. However the mechanisms of differentiation, migration and long term survival of the transplanted stem cells is still not clear. To address this question by the use of MRI we are magnetically labelling murine embryonic stem cells with iron-oxide particles (VSOP) *in vitro* and transplant the cells in the stratum of a Parkinson rat model. Additionally we examined for the first time whether incubation with VSOP can increase the cellular level of oxidative stress as oxidative stress may play a key role in the pathogenesis of Parkinson`s disease.

Subjects and Methods

Murine embryonic stem cells (CRL-1934, ATCC, Manassas, USA) were magnetically labelled *in vitro* with Very Small Super-Paramagnetic Iron-Oxide-Particles (VSOP) (Ferropharm, Teltow, Germany). The uptake of VSOP was measured by NMR *in vitro*. The level of oxidative stress was detected by measuring the level of malonyldialdehyde (MDA). Female Wistar rats were lesioned by intranigral injection of 6-OHDA. 1×10^5 magnetically labelled cells in 2 µl PBS were stereotactical transplanted into the striatum of the rats. High-resolution MR-imaging was performed using a 7T Bruker Pharmascan. T2* weighted images were acquired with an inplane resolution of 130 μm^2, using a 2D gradient echo sequence (TE 5.4 ms, TR 400.4 ms).

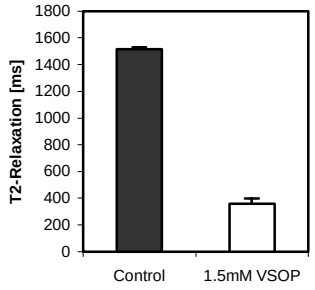

Fig.1 Relaxometry measurent of unlabelled (Control) resp. labelled stem cells

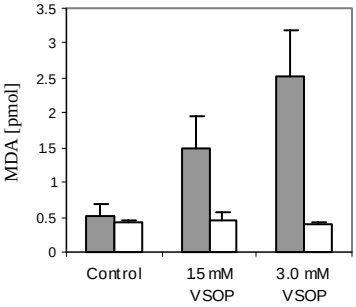

Fig.2 Oxidative stress directly (white bars) and 24h after incubation with VSOP (grey bars)

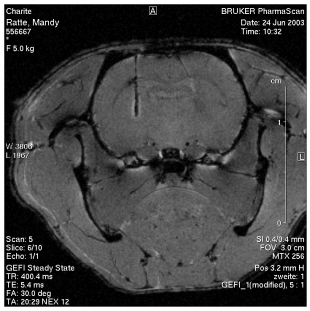

Fig.3 T2*-weighted MR-imaging at 7T 4 months after transplantation *in vivo*

Results

Incubation of embryonic stem cells with VSOP led to a highly significant uptake of iron, measured indirectly by the reduction of T2-time by NMR (Fig.1) and confirmed by atomic absorption spectroscopy (data not shown). However the incubation of cells with iron-oxide-particles also results in a highly significant augmentation of oxidative stress (Fig. 2 white bars). The decrease of oxidative stress to control levels one day after incubation (Fig. 2 grey bars) indicates that the increase of oxidative stress is transient and closely linked to the incubation of the cells with iron-oxide particles. *In vivo* MRI at 7T after intrastriatal transplantation of labelled stem cells led to characteristic signal extinctions in T2* weighted images. Four months after transplantation the labelled stem cells are still detectable and seem to show a migration along the corpus callosum (Fig. 3)

Discussion and Conclusion

Magnetic labelling of embryonic stem cells is a feasible tool for the monitoring of cell-based therapies. Even if the labelling does increase cellular stress the long term survival is not significantly affected. Cell migration has by this non-invasive MR-study shown to be an important issue concerning transplantation in PD. Further studies have to be conducted to assess migration dynamics and patterns.