Spectroscopic monitoring of an experimental brain lesion treated by cell transplantation

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Introduction

The adult CNS possesses a limited capacity for regeneration; however, new possibilities for repairing the nervous system have opened after the discovery of stem cells, which can not only differentiate into nerve cells but also produce different growth factors that facilitate regeneration. Recently, there have been several demonstrations that different types of stem cells can be transplanted successfully in animal models of disease or injury (for rev. see (1)). MRI is a powerful non-invasive tool for monitoring transplanted cells, but it requires labeling the cells using paramagnetic or superparamagnetic labels (2). Although MR spectroscopy (MRS) cannot directly localize the transplanted cells, it can provide insight into metabolic processes in the injured tissue after cell transplantation.

Subject and Methods

Twenty-two Wistar rats were used in the experiment: 10 healthy untreated controls and 12 animals with a photochemical lesion in the right cortex, induced by the interaction of an intravenously injected photosensitive dye (Bengal Rose) and light. Four animals with a lesion were treated with mesenchymal stem cells (MSC). A cell suspension of 2 million cells was injected into the femoral vein six days after lesion induction. The first MRS measurement was performed one day after cell injection and then weekly for one month. Spectra were acquired from the lesion and from the contralateral hemisphere. The spectra were obtained with a single-voxel STEAM sequence, with TE = 3 ms and TR = 5000 ms. The volume of interest was approximately 30 cubic mm for each hemisphere. Untreated animals were measured at the same time intervals, healthy controls only once. The spectra were evaluated using the LCModel (3) to obtain absolute metabolite concentrations.

Results

Concentrations of selected metabolites measured in the lesion of treated and untreated animals are plotted in graphs 1 – 3.

N-acetyl aspartate (NAA) was significantly higher one week after lesion induction (after cell transplantation) in MSC-treated rats compared to untreated ones. However, it remained lower by 10 % compared to the NAA concentration in control animals, even four weeks after lesioning. Untreated animals showed very low NAA concentration in the lesion after one week. The concentration increased during the experiment to values comparable to treated animals.

The concentration of glutamate (Glu) in cell-treated animals reached normal values after the first week. Untreated animals showed very low Glu concentrations in the same time period, which gradually increased and reached normal values after four weeks.

A significantly higher glutamine concentration (Gln) was found at the beginning of the experiment in untreated animals, which decreased to the values observed in treated animals after 4 weeks.

A normal concentration of creatine (Cr) was found one day after cell transplantation. The concentration then gradually decreased. Untreated animals had a low Cr concentration from the beginning of the experiment.

The taurine (Tau) and inositol (Ins) concentrations gradually increased throughout the experiment; insignificantly faster increase was found in the treated animals.

Choline (Cho) and GABA concentrations did not change significantly during the experiment and did not differ from those in control animals.

Discussion

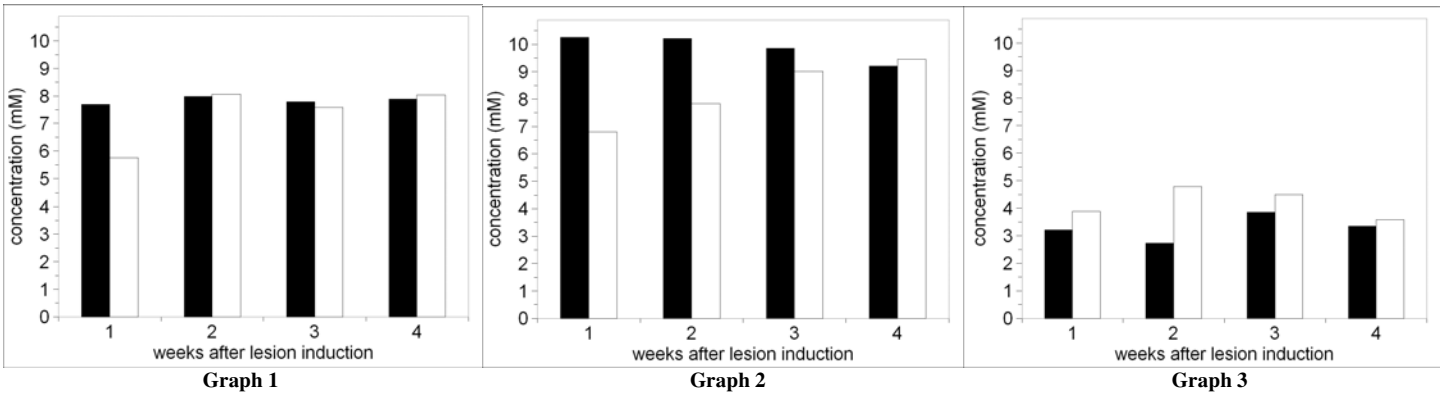
Although NAA is considered to be a neuronal marker, we cannot assume that the higher NAA concentration observed soon after cell transplantation means the immediate functional replacement of damaged tissue by the transplanted cells. However, the ability of MSCs to secret substances such as cytokines (interleukins) and trophic factors may facilitate regeneration and rescue partially damaged cells, which could lead to a faster recovery of the penumbral area of the lesion. Incomplete recovery is reflected by the fact that NAA concentration remains moderately decreased in both the treated and untreated groups compared to controls even after 4 weeks.

The low concentration of glutamate and the high concentration of glutamine (compared to controls) until the fourth week in untreated animals indicate pathological conditions in the tissue, corresponding to the high Glu/Gln ratio observed in other types of brain damage (3). Both glutamate and glutamine concentrations normalized after 4 weeks. The more rapid normalization of both Glu and Gln concentrations in the case of cell-treated animals is in accord with other tissue markers.

The time course of changes in the other observed metabolites supports a possible contribution of cell therapy to the healing process in brain tissue. The decrease in creatine concentration remains unexplained.

Conclusion

The experiment demonstrated a faster recovery of injured tissue in the presence of transplanted cells. Although we cannot expect complete recovery of the tissue within a short time period or the replacement of damaged neurons, transplanted cells applied soon after injury have an immunomodulatory effect and rescue partially damaged cells, resulting in a decrease in the penumbra area and enabling a more rapid regeneration of the tissue. MRS represents an interesting tool for monitoring the healing process and tissue regeneration.



Graph 1 **Graph 2** **Graph 3**

Graphs 1-3: Concentrations of N-acetyl aspartate (1), glutamate (2), and glutamine (3) measured in the lesion of treated (black bars) and untreated (white bars) animals 1, 2, 3, and 4 weeks after lesion induction.

References

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Acknowledgement

The study was supported by grants MZO 00023001, MSMT LC 554, ASCR 50390512