in vivo $^{1}H/^{13}C$ MRSI of changes in neurotransmitter metabolism in rats recovering from stroke

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Introduction

Stroke leads to structural and functional tissue injury involving distortion of key metabolic processes, such as oxidative glycolysis and neurotransmitter metabolism. Despite severe initial disability, most stroke subjects show at least some spontaneous functional recovery over time, which may be associated with brain plasticity.

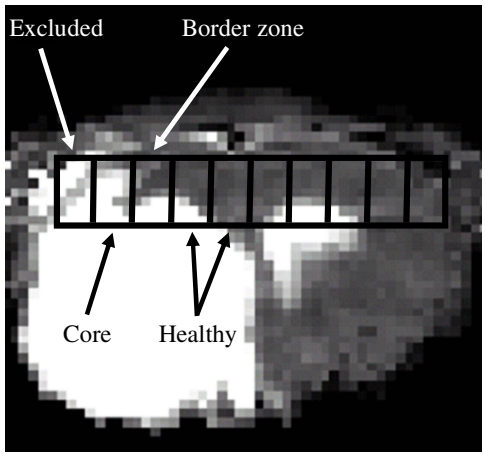

Fig 1. T_2 map of a coronal rat brain slice 3 weeks after stroke with the MRSI column overlaid, illustrating VOIs. The ischemic lesion is characterized by a prolonged T_2.

Structural and functional plasticity have been observed in tissue at the border of experimental ischemic lesions[1,2]. however, the metabolic basis thereof is largely unknown. Changes in neurotransmitter metabolism may play a key role in post-stroke recovery of brain function. To characterize metabolic alterations that may underlie restoration of tissue function, we applied $^{1}H/^{13}C$ MR spectroscopic imaging (MRSI) for *in vivo* detection of ^{13}C-labeled metabolic products after infusion of ^{13}C-labeled glucose. We hypothesized that initially impaired oxidative glycolysis and neurotransmitter metabolism in the lesion borderzone restored at chronic stages after stroke

Materials and Methods

Transient focal cerebral ischemia was induced in 14 male Wistar rats (200-250g) by 90-min occlusion of the right middle cerebral artery with an intraluminal filament.[3] MR experiments were performed at 24h (n=6) and 3 weeks (n=8) after stroke on a 11.74 T magnet (Magnex, Oxford, UK) equipped with a 9-cm diameter gradient set (max. 395 mT/m in 180 µs) interfaced to a Bruker Avance console. Rats were anesthetized, tracheotomized and mechanically ventilated with halothane in N_2O/O_2 (70:30). T_2 maps of 9 slices covering the MRSI volume were reconstructed from multi-echo EPI images (TR=2500 ms; echo spacing 25 ms; etl 8, matrix 64x64; resolution 0.3x0.3x1.0 mm^3). $^{1}H/^{13}C$ MRSI was performed in 10 volumes of 1x2x5 mm^3 in a horizontal column through dorsal ipsi- and contralateral cerebral cortex (Fig. 1) during infusion of [U-^{13}C]glucose (TR/TE=2500/14 ms; sw 6 kHz; 2048 acquisition points). Based on the T_2 maps, voxels were assigned to volumes-of-interest (VOIs): lesion core (T_2>mean contralateral T_2+2SD), lesion borderzone (voxel adjacent to core) and non-ischemic tissue (adjacent to borderzone) for the ipsilateral hemisphere. Contralateral counterparts served as control. Quantitative analysis of ^{1}H and $^{1}H/^{13}C$ MR spectra was done with a dedicated version of LCModel.[4] Fractional enrichment (FE) time curves for [4-^{13}C]Glu and [4-^{13}C]Gln were mono-exponentially fitted to calculate FE_{max} and $t_{1/2}$.

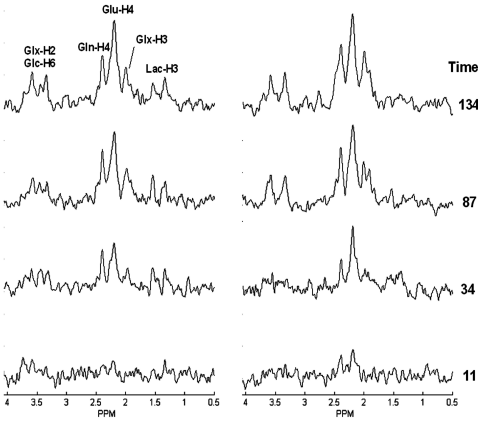

Fig 2. $^{1}H/^{13}C$ MR spectra from ipsi- (left) and contralateral (right) borderzone at different time-points after [U-^{13}C]glucose infusion, 24 h post-stroke

Results

At 24 h and 3 weeks after stroke, glutamine (Gln), choline (Cho) and NAA levels were significantly reduced in the lesion core compared to contralateral tissue, while lactate and lipids (Lac/Lip) signals were increased. In the borderzone Cho and NAA were significantly reduced at 24 h, while Gln and Lac/Lip were increased. After 3 weeks, Cho, NAA and Gln levels had normalized. Our dynamic $^{1}H/^{13}C$ MRSI experiment revealed minimal [4-^{13}C]Gln and [4-^{13}C]Glu formation in the lesion core, while the borderzone showed incorporation of ^{13}C label in several neurotransmitters (Fig. 2). Fig. 3 presents [4-^{13}C]Glu and [4-^{13}C]Gln turnover curves for all VOIs in a rat at 24 h after stroke. No [4-^{13}C]-Gln labeling could be detected in the core. We found a significant reduction of FE_{max} of Glu in the core and borderzone at 24 h after stroke, which had normalized in the borderzone after 3 weeks.

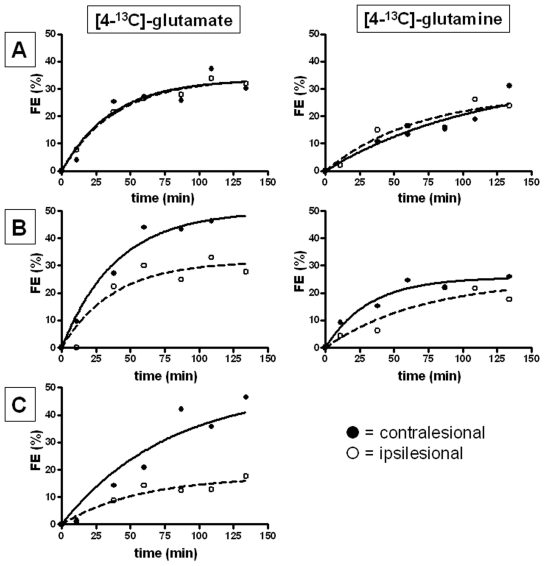

Fig 3. [4-^{13}C]Glu (left) and [4-^{13}C]Gln (right) turnover curves of ipsi- (—) and contralateral (---) healthy (A), borderzone (B) and core (C) at 24 h after stroke.

Discussion

We combined *in vivo* MRI and $^{1}H/^{13}C$ MRSI to characterize changes in metabolism in potentially functionally viable tissue around an ischemic lesion in rat brain. Semi-acutely after transient ischemia, reductions in NAA levels and Glu turnover suggest severe neuronal dysfunction in the lesion borderzone, outside the infarcted area. However at 3 weeks post-stroke, NAA levels as well as Glu turnover had normalized, indicative of neuronal recovery. Our findings indicate that early impairment of metabolic function in the morphologically intact lesion borderzone has the potential to recover over time, which may contribute to post-stroke functional improvement. Insights in the metabolic underpinning of restoration of tissue function may aid in development of therapeutic strategies to improve functional recovery after stroke.

References

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