Investigation of spatial distribution of metabolites in rat brain at elevated plasma glucose levels

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Introduction: Hyperglycemia has been reported to be associated with regional changes in glucose (Glc) concentrations in brain of healthy subjects and in the concentration of myo-inositol (Ins) in diabetic patients (1). Recurrent hyperglycemia also induced a decrease of glutamate (Glu), taurine (Tau), ascorbate (Asc) and an increase of phosphoethanolamine (PE) in hippocampus of developing rats (2). Spatial distribution of various metabolites in rat brain can be determined by means of short-echo-time (TE) proton spectroscopic imaging. Using this technique, the aim of this study was to investigate the effect of acutely increasing plasma Glc levels on *regional* brain concentrations of Glc, Glu, Ins, Tau, Asc, PE, glutamine (Gln), GABA, NAA, total creatine (Cr), choline (Cho) and macromolecules (Mac) in somatosensory and retrosplenial cortex, and in hippocampus and thalamus of healthy rats.

Experimental: The data were obtained from brain of five adult Sprague-Dawley rats. Hyperglycemia was induced by infusing 20 % Glc solution in the femoral vein at a rate of 0.8–2 mL/hour. Plasma Glc concentration was determined on an Analox GM7 analyzer (Analox Instruments, MA, USA) and was increased from 6.4–7.5 mmol/L (normoglycemia) to 19.0 mmol/L. Metabolic maps were obtained on a 9.4 T VNMRS scanner (Varian/Magnex Scientific) using a SPECIAL spectroscopy sequence (TR/TE = 2500/2.8 ms) with phase encoding in the coronal plane (Fig. 1). Reference water signals were measured using the same protocol without water suppression and with TR=1500 ms. A home-built 14 mm diameter quadrature coil was used as a transceiver. Field homogeneity was adjusted by FASTMAP (4). The region of interest used for constructing metabolic maps consisted of 7×12 voxels with a nominal voxel size of 0.75×0.75×2 mm^3 (1.1 μL). The *k*-space data were filtered with a Hanning function in two spatial domains (3). Using the water signal for each voxel, absolute concentrations of metabolites corrected for different T_1 of metabolites and water were calculated for individual voxels by LCModel (5).

Results: Fig. 1 shows a VOI and corresponding maps of Glc, Lac, Glu, Ins and Tau in a rat brain at euglycemia and hyperglycemia (plasma Glc concentrations about 7.0 and 19.0 mmol/L, respectively). The VOI included somatosensory and retrosplenial cortex, hippocampus and thalamus. While the increase of Glc was visible in all brain structures at hyperglycemia, Lac concentration increased in the region of the 3rd ventricle (more than 6 mmol/kg) and in hippocampus (4-5 mmol/kg). The maps of Glu, Ins and Tau did not show any markable difference at hyperglycemia and kept their specific spatial distribution patterns: a higher concentration of Glu (12-14 mmol/kg) in somatosensory cortex and in thalamus, a higher concentration of Ins in hippocampus (above 8 mmol/kg) and an increased Tau concentration in somatosensory cortex and hippocampus (above 7 mmol/kg) compared to retrosplenial cortex and thalamus (below 6 mmol/kg). Similarly, no substantial difference was observed in maps of NAA, Cr, Gln, GABA, Asc, PE and Mac at different plasma Glc concentrations (not shown). Fig. 2 shows plots of brain Glc concentration versus plasma Glc levels in cortex, hippocampus and thalamus. For all three brain structures as well as for averaged brain Glc concentrations a satisfactory linear fits were obtained. Differences in slopes of these fits were statistically insignificant. The Lac concentration at the highest plasma Glc concentrations (17.7 – 19 mM) was significantly higher than that at euglycemia ($p < 0.001$), however, its linear fit with the Glc plasma concentration was poor (R^2=0.3).

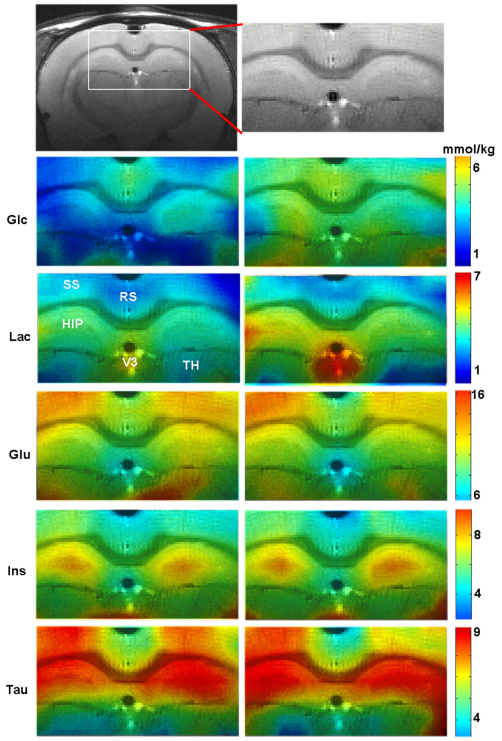

Fig. 1. Metabolic maps at euglycemia (left column) and hyperglycemia (right column). SS= somatosensory cortex, RS= retrosplenial cortex, HIP= hippocampus, TH= thalamus, V3= 3rd ventricle.

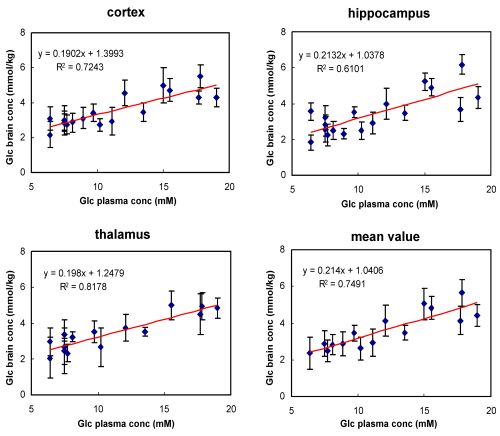

Fig.2. Glc concentration in various brain structures at different plasma Glc levels. Data points represent means ± SD of 4-11 voxels selected in the specified regions. The graph of mean values includes all selected voxels.

Discussion and Conclusions: High resolution metabolic maps of rat brain in the coronal orientation enabled to observe distribution of metabolites in various brain structures under increased plasma Glc levels. No difference in the dependence of brain Glc concentration on plasma Glc levels in cortex, hippocampus and thalamus was found. Thus, the Glc transport is probably similar in all three studied brain structures. The observed increase of Lac at increased plasma Glc levels can also be caused by other factors such as stress or impaired metabolism during long-term anesthesia. The absence of changes in the metabolic profile of normal brain at hyperglycemia indicates that tissue physiology should not be substantially affected by an acute hyperglycemic attack.

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