Region-specific cerebral metabolic changes in streptozotocin-induced T1DM rats revealed by in vivo ^{1}H-MRS

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Introduction In vivo ^{1}H MRS has been used to assess regional cerebral metabolic changes in type 1 diabetes mellitus (T1DM) patients and animal models. It has been shown that uncontrolled streptozotocin (STZ)-induced T1DM could result in rapid and long-lasting metabolic changes in the brain [1, 2, 3]. However, the results are sometimes contradictory. Biessels et al observed significantly reduced N-acetyl aspartate (NAA) level at hyperlycemia in a voxel containing cortex, striatum, thalamus and hippocampus at 2w after induction [1]. Durate et al, however, observed increased hippocampal NAA level at hyperglycemia 30d after induction [2]. In a voxel containing hippocampus and cortex, Wang et al didn't find significant changes in hyperglycemia NAA level until 45d after induction [3]. We hypothesize that at least some of the discrepancies may be due to the fact that T1DM-related cerebral metabolic changes are region-specific. In this study, we measured metabolic changes in the striatum, hippocampus and visual cortex of STZ-induced T1DM rats at 4 weeks (4w) after induction with in vivo ^{1}H MRS. The metabolic changes were compared among different brain regions.

Materials and methods Eight-week old male SD rats (232±15 g) were used. T1DM was induced by an intraperitoneal (i.p.) injection of STZ at a dose of 62 mg/kg body weight. The control animals (con, n=6) received the same amount of solvent. Only the STZ-treated rats with fasting blood glucose ≥11.3 mmol/L at 3d after induction were included (n=10). All spectra were acquired on a 7 T/20 cm Bruker Biospec scanner with a volume coil for RF transmission and a quadrature surface coil for detection. The animals were anesthetized with 1.8-2.5% isoflurane and injected with a single dose of insulin (0.5 U/ml, 4 ml) to reach euglycemia (blood glucose level: 7.6±2.1 mmol/L). Localized spectra were acquired from striatum, visual cortex and hippocampus of each animal starting at about 38 minutes after the insulin injection. A PRESS sequence was used with TR/TE 2500/15 ms, spectral bandwidth 4 kHz, 2048 data points and 256 averages. LCModel was used for quantification using the total creatine (tCr) concentration as the internal reference. Unless otherwise specified, only the fitting results with CRLB<15% were considered reliable and included in the analysis. Statistical analysis was performed with independent-sample t-tests. A $p<0.05$ with FDR correction for multiple comparisons was considered to be statistically significant.

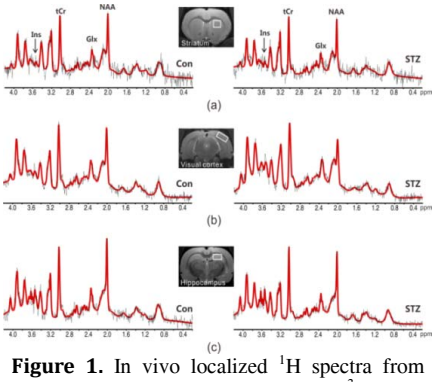

Figure 1. In vivo localized ^{1}H spectra from voxels in striatum (a, 2.5×1.8×2.5 mm^3), visual cortex (b, 4×1×4 mm^3) and hippocampus (c, 1×4×4 mm^3) of a control rat and a STZ-treated rat. The gray lines represent raw spectra, and the red lines represent the LCModel fits to the raw spectra. Glu: glutamate; Glx: Glu+glutamine; Tau: taurine; Ins: myo-inositol.

Results The STZ-treated animals had significantly lower body weight (218±30 vs. 365±20 g) and higher blood glucose level (26.7±7.0 vs. 4.0±0.5 mmol/L) at 4w, compared to control animals. Figure 1 shows the localized spectra and corresponding LCModel fits from a control rat and a STZ-treated rat. Figure 2 shows the quantitative results of relative metabolite concentrations. For the STZ-treated animals, Glu, NAA and tNAA levels were found to be significantly lower than control in the striatum and hippocampus, but not in the visual cortex; Tau and Ins levels were significantly higher only in the hippocampus, but not in the striatum and visual cortex; Glx remained unchanged in all three brain regions.

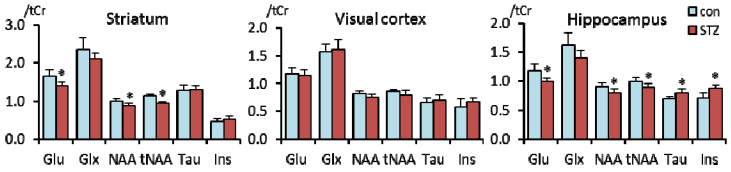

Figure 2. Quantitative metabolite concentrations. * denotes significantly different from control ($p<0.05$, FDR corrected). tNAA: NAA+N-acetyl aspartylglutamate.

Discussion Our results suggested that the metabolic changes in the brain of STZ-induced T1DM rats are region-specific at 4w after induction. The metabolic perturbations in hippocampus involved both neuronal markers (i.e., Glu and NAA) and osmolytes (i.e., Ins and Tau). In contrast, the visual cortex showed little metabolic changes. Interestingly, the diabetic striatum showed significant changes only in the neuronal markers, but not in the osmolytes. The metabolic changes in the brain of clinical T1DM patients also appeared to be region-specific. For instance, decreased NAA and increased Ins level were frequently observed in the frontal lobe and basal ganglia [4, 5], but not in the thalamus [6]. The regional-specific metabolic changes in T1DM brain could be due to the fact that, compared to the visual cortex, the hippocampus and striatum are more vulnerable to glucose toxicity and/or diabetes-related vascular complications.

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