Anatomical and Metabolic Changes in the Visual Cortex of Streptozotocin-treated Type 1 Diabetic Rats

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Introduction Diabetes mellitus (DM) is a lifelong metabolic disturbance. Diabetic retinopathy (DR) is one of the major complications of chronic diabetes, and a leading cause of blindness. Chronic diabetic patients often show impaired contrast sensitivity, deficits in perceptive resolution and night vision, and even visual loss [1]. Neuroimaging studies have revealed that chronic diabetic complications also include reduced grey matter density in the right occipital regions (type 1 DM) and reduced fractional anisotropy in the optic radiation (type 1 DM) [2,3]. In this study, we investigated chronic complications in the visual cortex of diabetic rats with high resolution anatomical imaging and in vivo ^{1}H MRS.

Materials and methods Eight-week old male Sprague-Dawley rats, weighing 202-278 g were used. Type 1 diabetes was induced by a single-dose intraperitoneal (i.p.) injection of streptozotocin (STZ, 62 mg/kg). Control animals received i.p. injection of the same amount of solvent (0.01 mol/L citric acid). The STZ-treated rats with fasting blood glucose < 12.4 mmol/L on day 3 were excluded from the study. All rats were scanned on a 7 T/20 cm Bruker Biospec scanner under isoflurane anesthesia (1.8-2.5%, in pure O_2). A volume coil was used for RF transmission, and a quadrature surface coil for signal detection. High resolution anatomical images were acquired with a RARE sequence with FOV 3.5 cm×3.5 cm, matrix size 512×384, slice thickness 0.58 mm, TR 5800 ms, TE_{eff} 40 ms, RARE factor 4 and a total of 8 averages. A PRESS sequence was used for in vivo ^{1}H MRS, with a 4 mm×1 mm×4 mm voxel placed on the visual cortex (Fig. 2b, white rectangle), TR/TE 2000/20 ms, spectral bandwidth 4 kHz, 2048 data points and 128 averages. All spectra from the STZ-treated rats were acquired at euglycemia (blood glucose level=7.9±1.1 mmol/L), at least 35 minutes after an intravenous bolus injection of 2.5 ml (2 U/ml) insulin. Peak heights were used to calculate metabolite level ratios.

Results Compared to the control rats (n=8), the STZ-treated rats (n=7) had significantly increased fasting blood glucose level (Fig. 1a), decreased body weight (Fig. 1b), and reduced thickness of visual cortex (Fig. 2b, 1.55±0.04 mm vs. 1.65±0.01 mm, $p<0.05$) at 12w after induction of diabetes. Another cohort of STZ-treated rats (n=6) did not show visual cortex thinning at 2w (Fig. 2b). Figure 3 showed ^{1}H spectra acquired from the visual cortex of a control rat and a STZ-treated rat at 12w. The STZ-treated rats showed significantly increased mI/Cre ratio (0.62±0.09 vs. 0.52±0.09, $p<0.05$) and significantly decreased NAA/Cre ratio (1.04±0.06 vs. 1.13±0.07, $p<0.05$) in the visual cortex at euglycemia (Fig. 4).

Discussion A previous study has showed that STZ-induced diabetic mice had significantly reduced cortex volume at 8 months [4]. Our results suggest that atrophy of the visual cortex may occur at earlier time. In addition to the anatomical changes, the visual cortex of diabetic rats also showed significant changes in metabolic profiles at euglycemia, such as increased mI/Cre ratio and decreased NAA/Cre ratio. Duarte et al. reported that, compared to control, the STZ-treated rats had significantly increased mI and NAA concentrations in the hippocampus at 30 days after treatment [5]. Increased mI level has also been reported in the occipital cortex of blind subjects [6] and in the white matter of DM patients [7]. We think that abnormal mI level in the visual cortex of the diabetic rats may have reflected glucose metabolic disorder and/or glia dysfunction in the region. Since NAA is a biomarker of neuronal density and/or function, reduced NAA/Cre in the visual cortex of the STZ-treated rats might indicate that the neurons in the region are affected by long-term hyperglycemia.

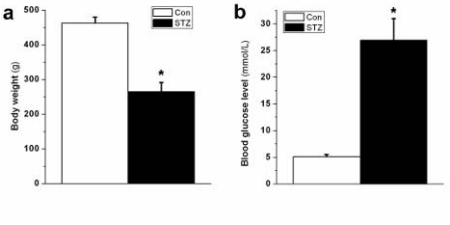

Figure 1. Compared to control (Con), the STZ-treated rats had significantly decreased body weight (a) and increased fasting blood glucose level (b) at 12w (*p<0.05).

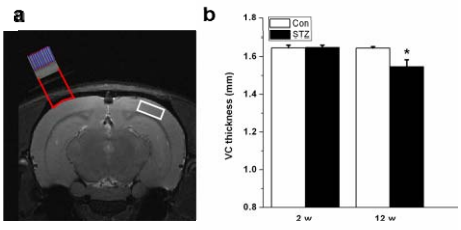

Figure 2. Compared to the control rats (Con), the STZ-treated rats had thinner visual cortex thickness at 12w after induction (b) (*p<0.05). The regions for cortex thickness measurement and ^{1}H-MRS are shown on the left and right hemispheres, respectively (a).

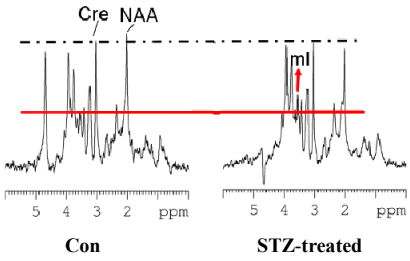

Figure 3. In vivo ^{1}H spectra from the visual cortex of a control rat (Con) and a STZ-treated rat at euglycaemia at 12 w after induction. mI: myo-inositol; Cre: creatine.

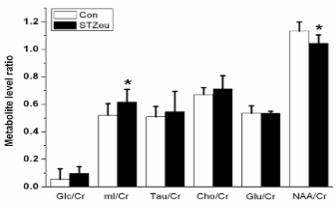

Figure 4. Compared to the control rats (Con), the STZ-treated rats showed significantly (*p<0.05) increased mI/Cre ratio and decreased NAA/Cre ratio in the visual cortex at euglycaemia.

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