Diffusion Abnormality in Olfactory Bulbs of Type-I Diabetic Rats

L. F. Gao[1], M. M. Huang[1], and H. Lei[1]

[1]State Key Laboratory of Magnetic Resonance and Atomic and Molecular Physics, Wuhan Institute of Physics & Mathematics, The Chinese Academy of Science, Wuhan, China, People's Republic of

Introduction It has been shown that diabetes mellitus (DM) patients are often associated with olfactory dysfunction [1,2]. It has been reported that axonal transport in the olfactory bulbs of streptozotocin (STZ)-treated diabetic mice is impaired [3]. In this study, diffusion tensor imaging (DTI) is used to assess axonal water diffusion abnormality in the olfactory system in type-I diabetic rats induced by STZ injections.

Materials and methods Animal preparation: Eight-week old male Sprague-Dawley rats, weighing 202-278 g, received intraperitoneal injections of either 62 mg/kg STZ dissolved in sodium citrate buffer (0.01 M, pH 4.5) (STZ group, n=10) or the same amount of sodium citrate buffer (control group, n=10). The treated animals were considered to be diabetic if their fasting blood glucose levels were higher than 223 mg/dl on day 3 after injections. MRI: MRI studies were performed at 2 weeks after diabetes induction on a 7.0 T/20 cm Bruker Biospec scanner with a 72-mm diameter volume coil for RF transmission and a quadrature surface coil for signal detection. High resolution anatomical images were acquired from axial slices of the olfactory bulb (OB) with a RARE sequence, TR 5800 ms, TE_{eff} 40 ms, matrix size 512×384, FOV 3.5 cm×3.5 cm, slice thickness 0.58 mm, RARE factor 4 and 8 averages. A spin-echo echo planar DTI sequence was used with the following acquisition parameters: TR 2000 ms, TE 26 ms, matrix size 128×128 (zero-filled to 256×256), FOV 3.0 cm×3.0 cm, slice thickness 0.8 mm, Δ 14 ms, δ 3 ms (b=0 and 800 s/mm^2) and 4 averages. The diffusion-weighting gradients were applied on 30 non-collinear directions for encoding scheme. Data processing: With the DTI mapping software (DTIstudio), the fractional anisotropy (FA) maps were obtained. The high resolution T_2 weighted images were used to define the regions of interest (ROIs) which were manually outlined on FA maps. To characterize the axonal transport in the ROIs of the olfactory bulbs quantitatively, four diffusion indices, including FA, mean appear diffusion coefficient (MD), axial diffusivity ($ADC_{//}$) and radial diffusivity ($ADC_{\perp}$) were calculated and compared between the diabetic and control groups with Student's *t*-tests.

Results Figure 1 showed a FA map (Fig. 1A) and T_2 weighted image (Fig. 1B) acquired from a control rat. The five histological layers (olfactory nerve layer: ONL, glomerulus layer: GL, external plexiform layer: EPL, granule cell layer: GCL and subependymal zone: SEZ) were outlined on the T_2 weighted image. The ONL and GL were included in the ROIs delineated on the FA map. Fig. 1C ploted the quantitative changes of FA (the lateral or medial average values), MD, $ADC_{//}$ and $ADC_{\perp}$ (the lateral average values) of bilateral OB. Compared to the control animals, the STZ-treated rats showed diffusion abnormalities in both the lateral and medial OB, indicated by the significantly reduced FA. Correspondingly, statistically significant increases in both MD and $ADC_{\perp}$ but no significant changes in $ADC_{//}$ were associated with hyperglycemia.

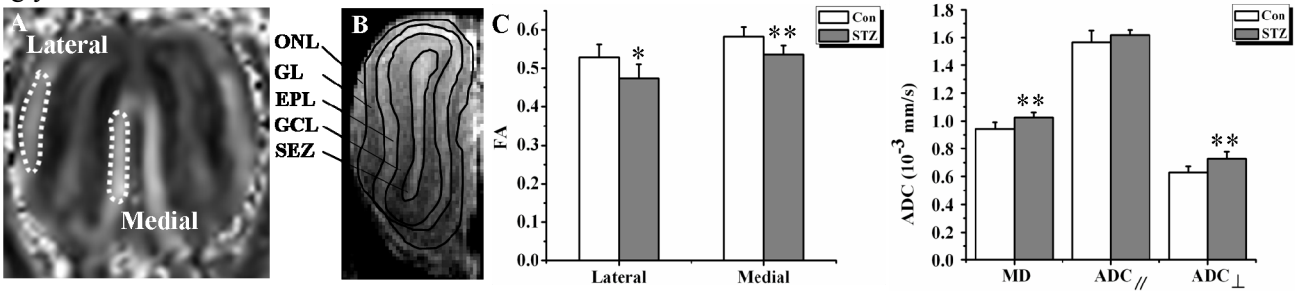

Figure 1 The ROIs (white dashed lines) on the FA map (A) included the olfactory nerve layer and glomerulus layer outlined on the high resolution T_2 weighted image (B) on the unilateral olfactory bulb (OB). In C, compared to the control animals, the STZ-treated rats had significantly reduced fractional anisotropy (FA) in both lateral and medial olfactory bulb (OB), and significantly increased mean appear diffusion coefficient (MD) and radial diffusivity ($ADC_{\perp}$), but no significant change in axial diffusivity ($ADC_{//}$) in lateral OB. (ONL: olfactory nerve layer, GL: glomerulus layer, EPL: external plexiform layer, GCL: granule cell layer, SEZ: subependymal zone) * p <0.01, ** p <0.001, compared to the control animals.

Discussion This result suggests the microstructure of the OB appear to be damaged as early as 2 weeks after STZ injections. In non-myelinated olfactory nerves, axonal membranes may play a role in anisotropic diffusion of water molecules [4]. The contribution of the deficit in axonal membranes and/or the loss of the neural fibres should be considered in the lower FA, higher MD and $ADC_{\perp}$ in the OB of the diabetic rats. In conclusion, the DTI technology can detect pathological abnormalities in axons in the OB, especially the ONL and GL, and provide further insights into mechanisms of olfactory dysfunction in diabetes.

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