Cerebrovascular damage after stroke in type two diabetic rats measured by MRI

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Introduction BBB damage and exacerbated secondary hemorrhagic transformation (HT) are consistent consequences of ischemic stroke in diabetic murine animals.[1, 2] However, prior preclinical studies only focused on the measurement of BBB disruption and cerebral vascular permeability rate at an early stage after stroke in diabetic animals using histological methods, which do not allow dynamic evaluation and application to patients. In the present study, by employing MRI, the temporal characteristics of BBB disruption were monitored weekly up to 5 weeks after stroke in the Type 2 diabetes mellitus (T2DM) and non-diabetic wild-type (WT) rats. These results could provide new information on dynamic and chronic cerebrovascular damages after stroke in T2DM rats.

Materials and Methods T2DM was induced in adult male Wistar rats.[3, 4] Blood glucose level was measured for confirmation of hyperglycemia. Right middle cerebral artery occlusion (MCAo) was then induced for 2 hours using the filament model. Reperfusion was initiated through removal of the thread and tying off the distal external carotid artery. Wistar rats, fed normal chow without Streptozotocin injection, received suture induced ischemia-reperfusion injury, and were used as the WT control rats. The control and T2DM animal groups were age matched. MRI was performed with ClinScan 7T system at one day and then weekly for 5 weeks after ischemia-reperfusion for all rats. After completing MRI scans, all animals (n=9 for T2DM and n=9 for WT rats) were euthanized 5 weeks post stroke. A birdcage type coil was used as the transmitter and a quardrature half-volume coil as the receiver. Pulse sequences included T_2-weighted imaging (T2WI), susceptibility weighted imaging (SWI) and contrast enhanced T_1-weighted imaging (CE-T1WI) with Gd-DTPA.

Results BBB disruption volumes of the T2DM rats measured with CE-T1WI exhibited significant differences from the WT rats. The volumes with Gd-DTPA enhancement were significantly ($p<0.05$) larger in the T2DM rats than in the WT rats from 1w to 5w after stroke, which indicates that BBB disruption was significantly worse in T2DM rats up to 5 weeks after stroke, compared to the WT rats (Fig.1). BBB disruption after ischemia may lead to HT. The hypointensity areas excluding veins in the SWI images are associated with hemorrhage. The representative T2DM and WT rats exhibited different evolutions of the HT after ischemia with SWI images in Figure 2. From the SWI images, areas of hypointensity which reflect hemorrhage, indicated by arrow heads in Fig.2, actively changed morphologically during 1d to 5w after stroke in the T2DM rat. While hemorrhage spots identified in the WT rat changed little; where hemorrhage was detected starting at 1w and no apparent change was subsequently found to 5w after stroke. The hypointensity areas are much larger in the T2DM rat than in the WT rat. Combining the histological results of H&E and Prussian blue staining for short- and long-term hemorrhage, respectively, the T2DM rat evidently had more severe and extensive hemorrhage after stroke than the WT rat, which coincided with the MRI measurements.

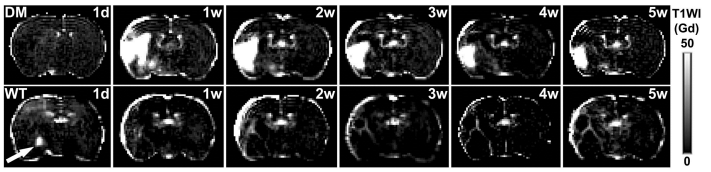

Fig.1 BBB disruption with Gd-DTPA enhancement in the subtracted images of CE-T1WI persisted from 1w to 5w post stroke in the T2DM rat (upper row). In

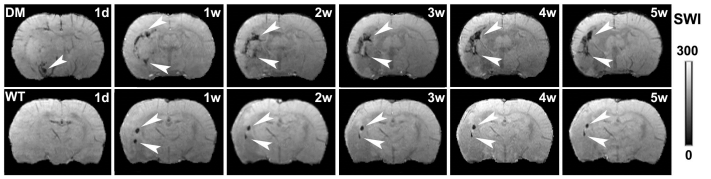

Fig.2 The hemorrhage after ischemia were demonstrated in SWI images for the representative T2DM (upper row) and WT (lower row) rats. Hemorrhagic spots were larger during 1d to 5w after stroke in the T2DM rat than in the WT rat.

Discussion BBB disruption and permeability rate in diabetic animals were regionally measured shortly after stroke from stained cerebral tissue sections, and measurements were limited to a one time measurement by using histological methods. MRI demonstrated that T2DM rats exhibited significantly larger volumes of BBB disruption starting from 1 week and persisted to 5 weeks after stroke ($p<0.005$), compared with WT rats. These data indicate that BBB disruption after stroke is a long-term problem in T2DM rats, which persists for at least 5 weeks after stroke. BBB disruption may lead to HT after ischemia. With the hemoglobin losing oxygen, diamagnetic oxyhemoglobin becomes paramagnetic deoxyhemoglobin. Phagocytic cells engulf the hemoglobin to degrade it, producing hemosiderin. Since deoxyhemoglobin and hemosiderin present after hemorrhage, SWI is employed to detect the hemorrhagic transformation after ischemia. Hemorrhagic volumes identified by SWI were significantly larger in T2DM rats than in WT rats from 1d to 5w after stroke ($p<0.05$). MRI results were consistent with histological measurements.

References

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