Cognitive Impairment is Associated with Neurovascular and White Matter Damage in Type II Diabetic Rats

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Diabetes mellitus is a common metabolic disease in the aged population and increases the risk of developing cognitive impairment and susceptibility to stroke. The cellular and molecular mechanisms underlying these processes are incompletely understood. Using a model of type 2 diabetes mellitus (T2DM), we investigated the effect of diabetes on neurovascular changes in relation to cognition in middle age rats. Morris water maze analysis showed that compared to age matched non-diabetic rats, middle aged T2DM rats exhibited spatial learning deficits. An odor recognition test which detects non-spatial memory deficits showed that T2DM rats failed to form new memories. In vivo dynamic Gd-DTPA contrast-enhanced magnetic resonance imaging (MRI) analysis revealed that compared to the non-DM rats, efflux of cerebrospinal fluid (CSF) contrast agent Gd-DTPA from the interstitial space in the hippocampus was substantially delayed in T2DM rats, which was confirmed by ex vivo confocal image analysis, indicating that T2DM impairs the glymphatic system that mediates clearance of the interstitial solutes in the brain. Cognitive deficits were highly and inversely correlated to the impairment of the glymphatic system. Immunohistological analysis showed the presence of microvascular leakage and loss of aquaporins-4, axons and oligodendrocytes in the hippocampi of T2DM rats. Focal cerebral ischemia in T2DM rats exacerbated sensorimotor and cognitive deficits during stroke recovery, although stroke did not increase infarction in T2DM rats compared to age-matched ischemic rats without diabetes. In addition, stroke further increased vascular leakage and reduced oligodendrocytes and myelinated axons within the hippocampi of T2DM rats. We found that the toll-like receptor/IL-1R-associated kinase signaling pathway activated by T2DM in cerebral endothelial cells mediates neurovascular damage. Collectively, our data indicate that T2DM induces neurovascular and white matter damage in the hippocampi and impairment of the glymphatic system, which may contribute to diabetes-induced cognitive deficits. Stroke exacerbates cognitive deficits.