Diabetic stroke

Macrovascular complications develop in over half of the diabetic individuals, resulting in high morbidity and mortality. This poses a severe threat to public health and a heavy burden on the social economy. It is therefore important to develop effective approaches to prevent or slow down the pathogenesis and progression of macrovascular diabetes mellitus complications (MCD).

Diabetes mellitus is a crucial risk factor for stroke and is associated with increased frequency and poor prognosis. Although endothelial dysfunction is a known contributor of stroke, the underlying mechanisms have not been elucidated

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Oxidative stress is a major contributor to MCD. Nuclear factor (erythroid-derived 2)-like 2 (NRF2) governs cellular antioxidant defense system by activating the transcription of various antioxidant genes, combating diabetes-induced oxidative stress. Accumulating experimental evidence has demonstrated that NRF2 activation protects against MCD. Structural inhibition of Kelch-like ECH-associated protein 1 (KEAP1) is a canonical way to activate NRF2. More recently, novel approaches, such as activation of the Nfe2l2 gene transcription, decreasing KEAP1 protein level by microRNA-induced degradation of Keap1 mRNA, prevention of proteasomal degradation of NRF2 protein and modulation of other upstream regulators of NRF2, have emerged in the prevention of MCD. This review provides a brief introduction of the pathophysiology of MCD and the role of oxidative stress in the pathogenesis of MCD. By reviewing previous work on the activation of NRF2 in MCD, we summarize strategies to activate NRF2, providing clues for the future intervention of MCD. Controversies over NRF2 activation and future perspectives are also provided in this review [1)].

In light of repeated translational failures with preclinical neuroprotection-based strategies, this preclinical study reevaluates brain swelling as an important pathological event in diabetic stroke and investigates underlying mechanism of the comorbidity-enhanced brain edema formation. Type 2 (mild), type 1 (moderate), and mixed type 1/2 (severe) diabetic mice were subjected to transient focal ischemia. Infarct volume, brain swelling, and IgG extravasation were assessed at 3 days post-stroke. Expression of vascular endothelial growth factor (VEGF)-A, endothelial-specific molecule-1 (Esm1), and the VEGF receptor 2 (VEGFR2) was determined in the ischemic brain. Additionally, SU5416, a VEGFR2 inhibitor, was treated in the type 1/2 diabetic mice, and stroke outcomes were determined. All diabetic groups displayed bigger infarct volume and brain swelling compared to nondiabetic mice, and the increased swelling was disproportionately larger relative to infarct enlargement. Diabetic conditions significantly increased VEGF-A, Esm1, and VEGFR2 expressions in the ischemic brain compared to nondiabetic mice. Notably, in diabetic mice, VEGFR2 mRNA levels were positively correlated with brain swelling, but not with infarct volume. Treatment with SU5416 in diabetic mice significantly reduced brain swelling. The study shows that brain swelling is a predominant pathological event in diabetic stroke and that an underlying event for diabetes-enhanced brain swelling includes the activation of VEGF signaling. This study suggests consideration of stroke therapies aiming at primarily reducing brain swelling for subjects with diabetes [2)].

Mishiro et al. examined the effect of hyperglycemia on hemorrhagic transformation at 24 hours after

middle cerebral artery occlusion (MCAO) in streptozotocin (STZ) -induced diabetic mice.

They also examined the effects of high-glucose exposure for 6 days on cell death, mitochondrial functions and morphology in human brain microvascular endothelial cells (HBMVECs) or human endothelial cells derived from induced pluripotent stem cells (iCell endothelial cells). Hyperglycemia aggravated hemorrhagic transformation, but not infarction following stroke. High-glucose exposure increased apoptosis, capase-3 activity, and release of apoptosis inducing factor (AIF) and cytochrome c in HBMVECs as well as affected mitochondrial functions (decreased cell proliferation, ATP contents, mitochondrial membrane potential, and increased matrix metalloproteinase (MMP)-9 activity, but not reactive oxygen species production). Furthermore, morphological aberration of mitochondria was observed in diabetic cells (a great deal of fragmentation, vacuolation, and cristae disruption). A similar phenomena were seen also in iCell endothelial cells. In conclusion, chronic hyperglycemia aggravated hemorrhagic transformation after stroke through mitochondrial dysfunction and morphological alteration, partially via MMP-9 activation, leading to caspase-dependent apoptosis of endothelial cells of diabetic mice. Mitochondria-targeting therapy may be a clinically innovative therapeutic strategy for diabetic complications in the future [3].

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