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Fan Fan

University of Mississippi Medical Center, USA

Disruption of actin cytoskeleton contributes to cerebral vascular dysfunction on Alzheimer-like cognitive deficits in diabetic T2DN rats

Diabetes mellitus is a leading risk factor for cerebrovascular disease and vascular cognitive impairment. However, the underlying mechanisms remain to be elucidated. The present study examines whether disruption of the actin cytoskeleton promotes cerebrovascular dysfunction in diabetic T2DN rat, and if this induces neurodegeneration and Alzheimer-like cognitive deficits. We found that F-Actin area distribution was significantly reduced in the vascular smooth muscle cells (VSMCs) freshly isolated from the middle cerebral arteries (MCAs) of T2DN rats compared with normal Sprague Dawley (SD) rats. The actin cytoskeleton was disrupted similarly in VSMCs treated with H₂O₂. Both young (4-month) and older (18-month) T2DN diabetic rats exhibit impaired pressure-induced myogenic response in isolated MCA. Forced dilatation occurred at pressures above 140 mmHg in MCAs isolated from elderly T2DN rats with mild hypertension but not controls. Cortical blood flow measured by laser Doppler flowmetry rose by 137±15% and 36±5%, respectively, in T2DN and SD rats when MAP was increased from 100 to 180 mmHg. Cerebral blood flow (CBF) auto-regulation was shifted to lower pressures in elderly hypertensive T2DN rats and they exhibited breakthrough at pressures above 140 mmHg. Levels of IL-1 β and IL-2, and the expression of amyloid β 42 (Aβ₄₂) and p-tau (S416) was significantly higher in the brains of T2DN vs. SD rats. T2DN rats exhibited neurodegeneration in the hippocampus and cortex. Elderly T2DN rats showed learning and short and long-term memory disabilities. Latency of escape were longer in an eight-arm water maze test in T2DN rats (2-hour: T2DN 96±12 vs. SD 13±3 seconds; 24-hour: T2DN 105±15 vs. SD 8±2 seconds), and they spent less time in the target arm 48 hours after removal of target platform (T2DN 3.4±2.6 vs. SD 45.0±1.7%). These results indicate that actin cytoskeleton is disrupted in cerebral VSMCs of diabetic T2DN rats, possibly due to elevated oxidative stress, and this contributes to impair of cerebral vascular function, neurodegeneration and Alzheimer-like cognitive deficits.

Biography

Fan Fan is an Assistant Professor at University of Mississippi Medical Center, USA. Her research focuses on the genetic basis of impaired myogenic response and auto-regulation of cerebral and renal blood flow and end organ damage in aging, hypertension and diabetes. She has published more than 40 papers in peer reviewed journals, and is currently serving as an Editorial Board Member and Reviewer for several journals. She is a Member of study sections in the Alzheimer's Association and American Heart Association. She is funded by the National Institute of Health and American Heart Association to study roles of Adducin gamma, CYP4A1 and 20-HETE on aging and hypertension related renal and cerebral vascular and dementia.

ffan@umc.edu

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