Dysfunctional cerebrovascular tone contributes to cognitive impairment in a non-obese rat model of prediabetic challenge: Role of suppression of autophagy and modulation by anti-diabetic drugs

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Abstract
Early stages of metabolic dysfunction, including prediabetes, pose a high risk for cardiovascular and cognitive impairment. While several pathological mechanisms linked advanced manifestations of metabolic deterioration, such as hypoglycemia, to neuronal inflammation and cognitive decline, little is known about the detrimental processes in effect at the early stages. To address this gap, we used a non-obese rat model of prediabetes developed in our laboratory. After 12 weeks of mild hypercaloric feeding, these rats developed hyperinsulinemia and increased fat/lean ratio without an increase in blood glucose level or body weight. These rats showed vascular dysfunction manifested as exaggerated contractility as a consequence of perivascular adipose inflammation. In this study, the mild metabolic challenge was associated with impaired hippocampal-dependent cognitive functions, spatial learning and memory and spontaneous object recognition. In line with our previous findings in this model, prediabetic rats had an augmented cerebrovascular myogenic tone demonstrated as an increased pressure-evoked contraction in pressure myography experiments on rat middle cerebral artery segments. The presumed brain hypoperfusion was accompanied by increased expression of hypoxia-inducible factor-1a in the hippocampus, together with markers of mitochondrial dysfunction and increased oxidative stress. In parallel, increased p62 expression and LC3 puncta in the prediabetic rat hippocampus, as well as increased Akt and mammalian target of rapamycin phosphorylation indicated a possible repression of autophagic flux. Consequently, the examination of the hippocampal CA1 area revealed increased CD68 and IBA-1 staining consistent with microglial activation and neuroinflammation, in addition to increased TUNEL staining and caspase-3 activity indicative of elevated neuronal apoptosis. Interestingly, a two-week treatment with non-hypoglycemic doses of metformin or pioglitazone, previously shown to improve adipose inflammation and vascular function, reversed the cerebrovascular and molecular alterations in the hippocampus. This was associated with an amelioration of cognitive function. The results of the present study indicate that early metabolic challenge leads to cerebrovascular alteration potentially leading to hippocampal hypoxia and mitochondrial dysfunction. Together with suppression of autophagy, these effects culminate in hippocampal inflammation and apoptosis possibly underlying the cognitive impairment.
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