Hippocampal abnormalities accompanying type 1 experimental diabetes: increased neuronal activation, astrocytic reactivity, oxidative stress and decreased neurogenesis

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Diabetes mellitus is associated with various cerebral disturbances in both humans and animals. Using two mouse models of type 1 diabetes, the nonobese diabetic (NOD) mouse, a recognized spontaneous model, and/or streptozotocin (STZ)-treated mice, a currently used pharmacological model, we previously described an upregulation of hypothalamic neuropeptides and a marked hippocampal astrogliosis, reflected by increased glial fibrillary acid protein-positive cells. Astrocytosis, a common feature to aging and neurodegenerative diseases, is often associated with neuronal dysfunction. Therefore, we investigated the possible alterations of astroglia and neurons in the hippocampus of STZ-treated diabetic female C57BL/6 mice one-month after injection. First, the number of Apolipoprotein-E^+ astrocytes, a well-accepted marker for neurodegeneration, was significantly increased below the hippocampal CA1 region. Second, we studied early gene products that are associated in the CNS with neuronal activation and events related to neurotoxicity and apoptosis. The number of neurons expressing the c-Jun protein was enhanced in pyramidal CA1 and CA3 and granular dentate gyrus (DG) layers of the hippocampus. The c-Fos protein expression and the activity of NADPH-diaphorase, an enzyme that is linked to NO production and oxidative stress, were also significantly augmented in the CA3 region. Third, the ability for neurogenesis in the DG and neuronal and/or glial phenotype was decreased by about 70%. These data indicate that hippocampal astrocytes and neurons are strongly activated one month after diabetes induction, exhibiting also higher oxidative stress. The proliferation of new neurons was strongly diminished. These results suggest the hippocampus as a crucial brain structure sensitive to abnormalities of glucose homeostasis. These alterations resemble those of an accelerated aging brain with all its pathological consequences.

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