Epigenetic impairments and α-synuclein mitochondrial accumulation associated with cognitive deficits in chronic hyperglycemia

Remor, A.P. ¹; Silva, R.A. ¹; Glaser, V. ¹; Matos, F.J. ¹; Ferreira, P.M.P. ¹; Prediger, R.D.S. ²; Rafacho, A. ³; de Paul, A.L. ⁴; Genti-Raimondi, S. ⁵; Aguiar, A. ¹; Latini, A. ¹

¹Departamento de Bioquímica, UFSC, Florianópolis, Brazil; ²Departamento de Farmacologia, UFSC, Florianópolis, Brazil; ³Departamento de Fisiologia, UFSC, Florianópolis, Brazil; ⁴Centro de Microscopia Eletrônica, UNC, Córdoba, Argentina; ⁵Centro de Investigaciones en Bioquímica Clínica e Inmunología, UNC, Córdoba

Diabetes mellitus is the most common metabolic disorder worldwide, and hyperglycemia appears to be associated with cognitive deficits and increased risk of dementia. Numerous metabolic and physiological changes promoted by chronic hyperglycemia are already characterized; however, cognitive deficiencies linked to epigenetic changes are virtually unknown. This study aimed to investigate the impact of chronic hyperglycemia on cognitive and biochemical parameters related to epigenetic modifications in the brain of streptozotocin (STZ-single intraperitoneal injection of 55 mg/kg)-induced hyperglycemic rats. The animals remained in these conditions during 10 and/or 60 days. The activity chamber, step-down inhibitory avoidance and water-maze tasks were performed. Additionally, the markers of oxidative stress status (NPSH; non-proteic thiol groups) and (TBARS; thiobarbituric acid-reactive substances), energy metabolism, insulin-mediated signaling transduction and DNA methylation profiles were evaluated in cerebellum, hippocampus and/or striatum of hyperglycemic and hyperglycemic-insulin (INS; 1.5 IU; human insulin; Novolin®N twice a day)-treated rats. It was shown that chronic hyperglycemia compromised short- and long-term memory, as well as spatial memory, effect that was accompanied by significant reduction of plasma antioxidant capacity and increased lipid peroxidation. Surprisingly, the hyperglycemic state induced a subcellular redistribution of hippocampal α-synuclein, even when the total content of the protein remained unchanged. Together, a specific and significant global DNA hypermethylation was observed in STZ-treated animals, in parallel with hypomethylation of LINE-1 region, effect that contributes to genome instability. REST gene expression was also significantly decreased in STZ-hyperglycemic group. In contrast, our results revealed that gene expression of the truncate splice variant REST4, was the opposite with REST level, accompanied by the hypermethylation in REST promoter in rat hippocampus after STZ-treatment. On the other hand, the INS administration significantly prevents these alterations. These data indicate that the compromised cognitive performance might be associated to increased brain inflammation, mitochondrial dysfunction and DNA hypermethylation triggered by persistent hyperglycemia.

Keywords: hyperglycemia; cognitive deficits; epigenetic alterations