Peripheral bioenergetics impairment induces a metabolic re-adaptation by regulatin creatine kinase (CK) activity and AMP-activated protein kinase (AMPK) signaling during chronic hyperglycemia

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Keywords: hyperglycemia, creatine kinase, energy metabolism
Founding: CNPq, CAPES and FAPESC

Diabetes mellitus is the most common metabolic disorder worldwide, and hyperglycemia appears to be the triggering factor in inducing debilitating vascular pathologies. This study aimed to investigate markers of brain energy metabolism in streptozotocin (STZ- single intraperitoneal injection of 55 mg/kg)-induced hyperglycemic rats. In order to evaluate the effect of the tight glucose control, the parameters were also assessed in rats receiving insulin (1.5 UI Novolin®N insulin, twice a day). The animals remained in these conditions during 10 and/or 60 days. A marked energy deficiency was observed in brain of STZ-animals as shown by the significant reduction in the activities of the electron transfer chain complexes I-IV and increased succinate-stimulated respiring state IV in STZ-rats. This impaired energetics was associated with increased brain creatine kinase (CK) activity, which was also confirmed in peripheral STZ-tissues as a possible compensatory mechanism induced by severe energy deficits in STZ-rat tissues. This appears to be associated with specific AMPK-dependent signaling alterations, since this kinase controls negatively CK activity by phosphorylation, and here phosphorylated AMPK was found to be significantly reduced in the periphery as well in the brain. Furthermore, the expression and the content of CK (cerebral isoform) was unchanged in STZ tissues. Considering that AGEs were accumulated in STZ brains (increased AGE immunecontent in brain preparations), and that oxidative stress was induced, it is feasible that AMPK could be also a cellular target for AGE formation, resulting in lower levels of active AMPK (phosphorylated AMPK), with a consequent re-adaptation of the brain and peripheral energy metabolism.