Mitochondrial Dysfunction In Brain Of Rats Submitted To An Animal Model of Phenylketonuria

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INTRODUCTION: Phenylketonuria (PKU) is characterized by accumulation of phenylalanine (Phe) in tissue and body fluids of affected patients. The main symptoms are related to brain injury, although the pathophysiology of this damage is poorly understood. **OBJECTIVE:** The aim of the present work was to investigate the *in vivo* effects of Phe on mitochondrial function in brain of young rats. **MATERIALS AND METHODS:** Animals received a single subcutaneous administration of 0.9 % NaCl (control group) or 5.2 µmol/g Phe plus 0.9 µmol/g p-chlorophenylalanine (PKU group). One hour after the administration, the animals were euthanized by decapitation and the cerebral cortex, striatum and hippocampus were isolated and homogenized. The activities of mitochondrial respiratory chain complexes I-IV and of citrate synthase (CS), isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), fumarase and creatine kinase (CK), as well as serum glucose levels, glycogen content and mitochondrial biogenesis proteins (TFAM, Nrf1 and PGC-1alfa) expression were determined. Student's *t* test was used for comparison between means. **RESULTS AND DISCUSSION:** It was observed that animals subjected to acute PKU presented a decrease of complex IV activity in striatum (control: 23.03 ± 6.05; PKU: 13.83 ± 3.80; $p<0.05$) when compared to control group. Furthermore, CK activity was inhibited (control: 2.99 ± 0.29; PKU: 2.43 ± 0.42; $p<0.05$) by Phe administration in cerebral cortex. On the other hand, no differences were found between groups in complex I, II, II-III, CS, IDH, SDH and fumarase activities and glucose serum levels and glycogen content, as well as mRNA levels of mitochondrial biogenesis proteins in any structure. **CONCLUSIONS:** Taken together, the present results indicate that Phe induces mitochondrial dysfunction. These data suggest that disturbances in cell bioenergetics homeostasis may contribute to the brain damage characteristic of phenylketonuric patients.

Keywords: brain; energy metabolism; mitochondrial function; phenylalanine; phenylketonuria

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