Alterations In BDNF Homeostasis In Brain Of Rats Submitted To An Animal Model Of Hyperphenylalaninemia

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INTRODUCTION: Hyperphenylalaninemia (HPA) is the hallmark of phenylketonuria (PKU), a genetic disorder caused by the deficiency of phenylalanine (Phe) hydroxylase. Brain injury is a clinical characteristic of PKU patients, although the pathophysiology of this damage is poorly understood. **OBJECTIVE:** The aim of the present work was to investigate the brain-derived neurotrophic factor (BDNF) levels in brain of rats submitted to an experimental model of HPA. **MATERIALS AND METHODS:** In this study, 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 (HPA group). One hour after the administration, the animals were euthanized by decapitation. The brain structures cerebral cortex, striatum and hippocampus were isolated and homogenized and BDNF levels, pro-BDNF, tropomyosin-related kinase B (TrkB) receptor and $p75^{NTR}$ relative messenger RNA levels, total and phosphorylated c-Jun N-terminal kinase (JNK), total and phosphorylated protein kinase C (PKC), tissue-type plasminogen activator (tPA) and p11 immunocontent were determined. **RESULTS AND DISCUSSION:** It was observed that animals subjected to acute HPA presented decreased BDNF levels in cerebral cortex, hippocampus and striatum, while pro-BDNF mRNA levels were increased in striatum. Furthermore, phosphoPKC/PKC ratio was decreased in cerebral cortex and hippocampus of HPA group, probably due to the decrease of BDNF signaling. On the other hand, TrkB and $p75^{NTR}$ (BDNF and pro-BDNF receptors, respectively) mRNA expression, and tPA, p11 and phosphoJNK/JNK immunocontent were not altered by high Phe levels in any structure. **CONCLUSIONS:** Taken together, our results suggest that Phe induces alteration in BDNF homeostasis. Since this neurotrophic factor plays a fundamental role in brain development and plasticity, contributing to synaptogenesis, synaptic plasticity, cognitive functions and memory, it is tempting to speculate that BDNF alterations might contribute to the intellectual deficiency observed in PKU patients.

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