CHRONIC TREATMENT WITH METHYLPHENIDATE INCREASES GLUTAMATE LEVELS IN CEREBROSPINAL FLUID AND IMPAIRS GLUTAMATERGIC HOMEOSTASIS IN PREFRONTAL CORTEX OF JUVENILE RATS

Schmitz, F.¹; Pierozan, P.¹; Rodrigues, A.F.¹; Biasibetti, H.¹; Coelho, D.M.²; Mussulini, B.H.³; Pereira, M.S.L.³; Parisi, M.M.⁴; Barbé-Tuana, F.⁴; de Oliveira, D.L.³; Vargas, C.R.²; Wyse, A.T. S¹

¹Universidade Federal do Rio Grande do Sul (Departamento de Bioquímica, Laboratório de Neuroproteção e Doenças Metabólicas), ²Universidade Federal do Rio Grande do Sul (Serviço de Genética Médica, Hospital de Clínicas de Porto Alegre), ³Universidade Federal do Rio Grande do Sul (Departamento de Bioquímica, Laboratório de Sinalização Glutamatérgica), ⁴Universidade Federal do Rio Grande do Sul (Departamento de Bioquímica, Laboratório de Biologia Molecular)

Understanding the consequences of chronic treatment with methylphenidate is very important since this psychostimulant is extensively prescribed to preschool age children. Additionally, little is known about the mechanisms underlying the persistent changes in behavior and neuronal function related with the use of methylphenidate. In this study, we investigate the effect of chronic treatment with methylphenidate in juvenile rats on the amino acids profile in cerebrospinal fluid, as well as on glutamatergic homeostasis, Na⁺,K⁺-ATPase function and balance redox in prefrontal cortex. Wistar rats at early age received intraperitoneal injections of methylphenidate (2.0 mg/kg) or an equivalent volume of 0.9% saline solution (controls), once a day, from the 15th to the 45th day of age. Twenty-four hours after the last injection, the cerebrospinal fluid and prefrontal cortex were removed and processed according to each analysis. Student's t test was used to evaluate the different parameters after the dates presented a normal distribution in Shapiro–Wilk test. Methylphenidate altered amino acid profile in cerebrospinal fluid, increasing the levels of glutamate. In the prefrontal cortex, methylphenidate administration was able to decrease the glutamate uptake, with no changes in GLAST and GLT-1; and the activity and immunocontent of catalytic subunits (α₁, α₂ and α₃) of Na⁺,K⁺-ATPase. We also observed changes in α₁ and α₂ gene expression of catalytic α subunits of Na⁺,K⁺-ATPase, decrease in sulfhydryl content, CAT activity and SOD/CAT ratio in juvenile rat prefrontal cortex treated with methylphenidate. Together, our results, suggest that chronic treatment with methylphenidate at early age induces excitotoxicity, at least in part, due to inhibition of glutamate uptake probably caused by disturbances in the Na⁺,K⁺-ATPase function and/or protein damage observed in the prefrontal cortex. These findings provide new basis for understanding of known biochemical and behavioral changes associated with chronic use of MPH during the development of central nervous system.

Key Words: psychostimulant; excitotoxicity; Na⁺,K⁺-ATPase