Ontogenetic expression of the glutamate receptors NR2A, NR2B, GluR 2/3 and GluR 6/7 in striatum and cerebral cortex of the knockout mice model of glutaric aciduria type I

Eichler, P.¹; Seminotti, B.¹; Ritter, L.¹; Hansel, G.¹; Souza, D.O.G.¹; Wajner, M.¹,²

¹Departamento de Bioquímica, ICBS, UFRGS, Porto Alegre, RS, Brazil; ²Serviço de Genética Médica, HCPA, Porto Alegre, RS, Brazil.

Glutaric acidemia type I (AG I) is a neurometabolic disease caused by deficiency of glutaryl-CoA dehydrogenase (GCDH) activity, leading to accumulation of glutaric (AG) and 3-hydroxyglutaric (3HG) acids in tissues and biological fluids of affected patients. Affected individuals present encephalopathic crises with striatal destruction between 6 and 36 months of age. Although the pathophysiology of this disorder is poorly known, previous works have shown neurotoxic effects of AG and 3HG. Some authors suggest that excitotoxicity may be one of the underlying pathomechanisms leading to brain damage in this disorder because AG and 3HG have structural similarity to glutamate. Our goal in the present work was to investigate the ontogenetic expression of the glutamate receptors NR2A, NR2B (NMDA receptors), GluR2/3 (AMPA receptors) and GluR6/7 (kainate receptors) in GCDH knockout mice at 7, 14, 30 and 60 days of postnatal life (P7, P14, P30 and P60) by western blotting. In the striatum, the expression of all receptors studied was lower in P60 knockout animals and there was a tendency to decrease the expression of NR2A and GLUR6-7 along time relatively to the wild type mice. In contrast, no alteration was detected on the expression of these receptors at P7. In cerebral cortex, there was a gradual decrease of GluR 6/7 expression along time, as well as a reduction of GluR 2/3 at P30 and of NR2B at P14 and P30. These data reveal alterations in the expression of NMDA, AMPA and kainate receptors that may result in neurotransmission impairment in AG I.

Key Words: glutamate receptors, striatum, cerebral cortex, glutaric acidemia type 1

Financial support: Research grants from CNPq, PROPESq/UFRGS, FAPERGS, PRONEX, FINEP Rede Instituto Brasileiro de Neurociência (IBN-Net) # 01.06.0842-00, Instituto Nacional de Ciências e Tecnologia-Excitotoxicidade e Neuroproteção (INCT-EN).