PROINFLAMMATORY RESPONSE IN CORTICAL ASTROCYTIES CAUSED BY
THE MAJOR METABOLITES ACCUMULATING IN HMG-COA LYASE
DEFICIENCY: THE ROLE OF ERK SIGNALING PATHWAY IN CYTOKINE
RELEASE

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Introduction: 3-Hydroxy-3-methylglutaric aciduria (HMGA) is an inherited metabolic disorder caused by 3-hydroxy-3-methylglutaryl-CoA lyase deficiency. It is biochemically characterized by predominant tissue accumulation and high urinary excretion of 3-hydroxy-3-methylglutarate (HMG) and 3-methylglutarate (MGA), as well as 3-methylglutaconate and 3-hydroxyisovalerate. Patients commonly present acute symptoms during metabolic decompensation, including vomiting, seizures and lethargy/coma accompanied by metabolic acidosis and hypoketotic hypoglycaemia. Although neurological manifestations are common, the pathogenesis of brain injury in this disease is poorly known. Astrocytes are important for neuronal protection and are susceptible to damage by neurotoxins.

Objectives: Our purpose was to investigate the effects of HMG and MGA on important parameters of redox homeostasis, cytokine production, mitochondrial function (MTT reduction) and viability (propidium iodide incorporation, PI) in cortical cultured astrocytes. Material and Methods: We isolated cerebral cortex from male neonate Wistar rats to cultivate astrocytes. The cells were cultured under standard conditions and incubated in the absence or presence of HMG or MGA (0.2 to 5 mM) for 24 h. We evaluated intracellular ROS production by 2\textsuperscript{-}7\textsuperscript{-}dichlorofluorescein diacetate (DCFHDA) oxidation, mitochondrial function by MTT reduction assay, reduced glutathione (GSH) content, IL-1\textbeta, IL-6, TNF-\alpha and NF\kappaB levels, astrocyte viability by PI and GFAP quantification by western blot analysis. Results and Discussion and Results: Both organic acids decreased astrocytic mitochondrial function and GSH concentrations, without altering cell viability. In contrast, they increased reactive species formation (DCFHDA oxidation). They also provoked a significant increase of IL-1\textbeta, IL-6 and TNF\alpha release through the ERK signaling pathway. Conclusions: Taken together, the data indicate that the principal compounds accumulating in HMGA induce a proinflammatory response in cultured astrocytes that may possibly be involved in the neuropathology of this disease.

Financial support: CNPq, PROPESq/UFRGS, FAPERGS, FINEP IBN-Net and INCT-EN

Keywords: 3-Hydroxy-3-methylglutaric aciduria; oxidative stress, proinflammatory response.