P-123 - METHYLMALONIC ACID COMPROMISES ENERGY METABOLISM AND GLUTAMATE UPTAKE IN C6 RAT ASTROGLIAL CELLS

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INTRODUCTION: Methylmalonic acidemia is an organic acidemia caused by deficient activity of L-methylmalonyl-CoA mutase or its cofactor cyanocobalamin and it is biochemically characterized by an accumulation of methylmalonic acid (MMA) in tissue and body fluids of patients. The main clinical manifestations of this disease are neurological and observable symptoms during metabolic decompensation are encephalopathy, cerebral atrophy, coma, and seizures, that commonly appear in newborns. OBJECTIVES: The aim of this study was to investigate the toxic effects of MMA in an astroglial cell line presenting astrocytic features. METHODOLOGY: Astroglial C6 cells were exposed to MMA (0.1-10mM) for 24 or 48 hours and cell toxicity, glucose consumption and mitochondrial metabolic function were analyzed. Cell viability and glucose uptake were determined by MTT reduction and glucose oxidase assays, respectively. Mitochondrial metabolic function was determined by measuring the oxygen consumption rate. Glutamate uptake was evaluated with L-[2,3-3H] glutamate. RESULTS: MMA significantly reduced cell viability after 48-hour period and increased glucose consumption during the same period of incubation. Regarding the energy homeostasis, MMA (5-10 mM) significantly reduced basal respiration of cells after 48-hour exposition. Moreover, maximal respiration was reduced after exposition to MMA in all tested concentrations. Finally, MMA significantly reduced glutamate uptake in C6 rat astroglial cells after 48-hour exposition period. DISCUSSION: MMA altered C6 rat astroglial cell viability and glucose consumption, suggesting that this organic acid compromises viability and stimulates anaerobic glycolysis. In addition, cell respiration was reduced after exposition to MMA, indicating that cell metabolism is compromised at resting and reserve capacity state, which might influence the cell capacity to meet energetic demands. Glutamate uptake was also compromised after exposition to MMA, which can be influenced by the impairment on cells energetic metabolism, affecting the functionality of the astroglial cells. Our findings suggests that these effects could be involved in the pathophysiology of neurological dysfunction of this disease. Acknowledgments: This study was supported by grants from FAPESP (2015/25541-0), CAPES and UFABC.