2-Methylcitric acid-induced disruption of bioenergetics is mediated by inhibition of glutamate dehydrogenase activity and induction of mitochondrial permeability transition in brain of young rats

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Introduction: Tissue accumulation of 2-methylcitric acid (2MCA) is usually observed in methylmalonic and propionic acidemias, which are clinically characterized by vomiting, psychomotor delay and neurological abnormalities. Objectives Considering that the pathogenesis of brain damage in these diseases are still poorly established and very little is known about the toxicity of 2MCA, the present study evaluated the effects of this organic acid on bioenergetics parameters in mitochondrial preparations from rat brain. Materials and methods: We evaluated the respiratory parameters states 3 and 4, respiratory control ratio (RCR) and uncoupled state, as well as glutamate dehydrogenase (GDH) activity, ATP production, mitochondrial membrane potential (ΔΨm) and swelling. Results: It was found that 2MCA (1 mM) significantly inhibited state 3 and uncoupled respiration, and decreased the RCR in glutamate respiring mitochondria. Furthermore, 2MCA-induced inhibition of state 3 respiration increased in parallel with glutamate concentration and respiration rate. We also observed that 2MCA also inhibited GDH activity that may be related in part to the reduction of state 3 respiration. It was also verified that 2MCA markedly decreased the ATP formation in glutamate plus malate-supported mitochondria, highlighting its potent property as a metabolic inhibitor. Finally, 2MCA provoked a significant decrease of ΔΨm and induced swelling in Ca²⁺-loaded mitochondria that were totally prevented by cyclosporine A plus ADP and ruthenium red, indicating that this organic acid induces mitochondrial permeability transition (MPT). Conclusions: Taken together, our data strongly indicate that 2MCA acts as a metabolic inhibitor of glutamate oxidation in part by inhibiting GDH activity, as well as a MPT inductor, disturbing mitochondrial energy homeostasis. We therefore presume that these deleterious effects may compromise brain energy metabolism and contribute to explain the pathogenesis of brain damage presented by patients affected by methylmalonic and propionic acidemias. Acknowledgements: CNPq, PROPESeq/UFRGS, FAPERGS, FAPESP, FINEP IBN-Net and INCT-EN Keywords: mitochondrial respiration; glutamate oxidation; 2-methylcitric acid