P-144 - ETHYLMALONIC ACID INDUCES BIOENERGETIC DYSFUNCTION IN RAT CEREBELLUM BY DISTURBING MITOCHONDRIAL SUCCINATE UPTAKE

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BACKGROUND: Ethylmalonic encephalopathy (EE) is a devastating neurometabolic disorder caused by mutations in the ETHE1 and biochemically characterized by ethylmalonic acid (EMA) accumulation. Individuals affected by EE present with chronic circulatory and gastrointestinal problems, and severe neurological symptoms, whose pathophysiology is not totally established. Therefore, we investigated the effects of EMA on mitochondrial bioenergetics and redox homeostasis in cerebellum of rats. ***METHODS:*** Mitochondrial preparations or supernatants were prepared from cerebellum of 30-day-old Wistar rats and used for the evaluation of EMA effects (2.5-5 mM) on mitochondrial respiration (states 3, 4, respiratory control ratio and uncoupled state) and membrane potential, glutathione (GSH) concentrations, malondialdehyde (MDA) levels, and aconitase, citrate synthase and respiratory chain complex II activities. ***RESULTS:*** Our results demonstrated that EMA decreased state 3, respiratory control ratio and uncoupled state in succinate-supported mitochondria. Inhibitory effects elicited by EMA on succinate-supported respiration were attenuated by nonselective permeabilization of the mitochondrial membrane, suggesting that succinate transport is impaired. We also verified that EMA dissipated mitochondrial membrane potential, which was prevented by cyclosporine A plus ADP and ruthenium red. EMA further decreased aconitase activity. However, MDA levels, GSH concentrations and citrate synthase activity were not altered by this organic acid. ***DISCUSSION:*** Our findings indicate that EMA impairs mitochondrial succinate uptake and induces mitochondrial permeability transition in cerebellum. It is presumed that these pathomechanisms underlie the neurological dysfunction observed in EE. Financial support: CNPq, CAPES, Propesq-UFRGS, FAPERGS, INCT-EN.