In Vitro Evidence that 3-Methylcrotonylglycine Accumulated in 3-Methylcrotonyl-CoA Carboxylase Deficiency Impairs Bioenergetics in Heart of Young Rats

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Deficiency of 3-methylcrotonyl-CoA carboxylase activity (3-MCCD) is an inherited metabolic disease of leucine catabolism biochemically characterized by accumulation of 3-hydroxyisovalerate (3-HIV),3-methylcrotonylglycine (3-MCG) and 3-hydroxyisovaleryl-carnitine (C5-OH).The clinical presentation is characterized by severe neurologic abnormalities and cardiomyopathy. Considering that the mechanisms of cardiomyopathy in 3-MCCD are unknown, the objective of the present study was to investigate the in vitro effects of 3-MCG (0.1 - 5mM) on important parameters of energy metabolism in heart of 30-day-old rats. Animals were sacrificed by decapitation and heart was isolated and used for the biochemical assays. Our results demonstrate that 3-MCG does not change CO₂ production. However, the activity of the respiratory chain complex IV was reduced by 3-MCG, with no alteration of the activities of complexes II, I-III, and II-III. In addition, mitochondrial creatine kinase (CK) was inhibited by 3-MCG, whereas cytosolic CK was not modified. Furthermore, antioxidants were capable of preventing the effect of 3-MCG on the activity of mCK, suggesting the involvement of reactive species on this inhibitory effect. Our results indicate that 3-MCG impairs heart bioenergetics at the level of energy formation and transfer. It is therefore presumed that these mechanisms may be involved in the pathophysiology of the cardiomyopathy presented by patients affected by 3-MCCD.

Keywords: cardiomyopathy, energy metabolism, 3-methylcrotonylglycine

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