Neurodegeneration in methylmalonic acidemia seems to be a consequence of mitochondrial energy impairment, possibly related to methylmalonic acid (MMA) accumulation. In this study we evaluated the effect of MMA on mitochondrial glutamate oxidative metabolism. MMA (1-10 mM) significantly inhibited glutamate-supported respiration by brain mitochondria. Glutamate transport measurements revealed that MMA effect on glutamate-supported respiration is not due to the inhibition of mitochondrial substrate uptake. MMA effect on the activity of enzymes related to neuronal glutamate metabolism was also evaluated. MMA showed minimal inhibitory effect on glutamate dehydrogenase and aspartate transaminase. α-Ketoglutarate dehydrogenase activity was significantly inhibited by MMA (Ki = 6.45 mM). α-Ketoglutarate transport measurements showed that extramitochondrial MMA exchanges with intramitochondrial α-ketoglutarate, depleting this substrate and consequently causes inhibition of glutamate-supported respiration. In addition, MMA inhibition of respiration by rat brain tissue fragments was partially prevented by malate. MMA \textit{in vivo} effects were studied by measuring respiration of isolated brain mitochondria from young rats chronically injected (ip, 15 d) with MMA. No difference was observed between control and MMA-treated samples, indicating that \textit{in vivo} MMA treatment does not lead to permanent mitochondrial dysfunction. Taken together, these results can contribute to a better understanding of mitochondrial dysfunction that occurs in methylmalonic acidemia as well as on its importance in the pathophysiology of this disease.

Keywords: metabolism, methylmalonate, mitochondria.

Supported by \textit{FAPESP} and \textit{CNPq}. 