Neuronal Damage Promoted by Ca\(^{2+}\) and Methylmalonic Acid Involves Mitochondrial Permeability Transition and Is Prevented by MitoK\(_{\text{ATP}}\) Channel Activation

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Methylmalonic acidemia is an inherited metabolic disorder that leads to brain damage associated to the accumulation of methylmalonic acid and impairment of energy metabolism. We studied the mechanisms by which methylmalonate (MMA) affects rat brain mitochondrial function and neuronal survival. At concentrations which inhibit respiration by 50%, MMA induced mitochondrial inner membrane permeabilization when in the presence of micromolar Ca\(^{2+}\) concentrations. ADP, cyclosporin A and catalase prevented or delayed this effect, indicating it is mediated by reactive oxygen species and mitochondrial permeability transition (PT). In addition to isolated mitochondria, we determined the effect of MMA on cultured PC12 cells and freshly prepared rat brain slices. MMA promoted cell death in striatal slices and PC12 cells, in a manner attenuated by the PT inhibitors cyclosporin A and bongkrekate and by diazoxide, an agonist of mitochondrial ATP-sensitive K\(^+\) channels (mitoK\(_{\text{ATP}}\)). The neuroprotective effect of diazoxide was reversed by 5-hydroxydecanoate, a mitoK\(_{\text{ATP}}\) antagonist, confirming it occurs due to the activity of this channel. Interestingly, we found that the mitochondrial inner membrane potential within intact cells treated with MMA was maintained in part by the reverse activity of ATP synthase (ATP hydrolysis), and that diazoxide prevented the formation of the membrane potential in the presence of MMA indirectly by decreasing mitochondrial ATP hydrolysis. We propose that neurodegeneration observed in methylmalonic acidemia involves the induction of PT. Under these conditions, activation of mitoK\(_{\text{ATP}}\) prevents neuronal cell death.

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