The Role of Mitochondria in Acetyl-L-Carnitine Neuroprotective Action

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Introduction: It is widely known that a number of chronic neurodegenerative disorders are related with dysfunctional mitochondria. Although it has been proposed that Acetyl-L-Carnitine (ALC) confers neuroprotection through mitochondria viability improvement, little is known concerning the molecular mechanisms involved. We propose to characterize the action of ALC in mitochondria bioenergetics and functional integrity.

Material and Methods: The rat pheochromocytoma cell line (PC12) is often used as an in vitro model to study the dopaminergic function. Here, PC12 cells were exposed to the toxic effects of methamphetamine (METH 1 and 100 µM) and pretreated with increasing doses of ALC (0.01, 0.1 and 1.0 mM). After 24 or 72h of incubation, mitochondrial membrane integrity and mitochondrial mass were assessed by using, respectively, Mitotracker CMXRos (2 µM) and Mitotracker Green (800 nM) by flow cytometry. Efficiency of glucose utilization was also assessed by incubating the cells with 37 kBq/mL of ^{18}F-FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose) in a low glucose serum-free medium for 60 minutes. The total protein content was assessed.

Results: Although ALC by itself did not improve mitochondrial function, ALC (0.01mM and 0.1mM) was effective in preventing the decrease induced by a 72h exposure to METH ($p<0.001$). Regarding mitochondrial mass, ALC in higher doses seems to induce a transitory increase of mitochondria mass ($p<0.05$). Furthermore, while a prolonged exposure to high levels of METH decreased mitochondria mass ($p<0.001$) pretreatment with ALC prevented this effect. Concerning the glucose metabolism, we observed an

increment on glucose uptake 24h after treating the cells with ALC 0.01 mM ($p<0.05$). This was even more pronounced when cells were also exposed to METH 100 µM ($p<0.01$). At 72h, cells treated with ALC 1.0 mM presented a significant increased glucose uptake in all tested conditions. While this may partially reflect increased energy use, it may also be caused by altered membrane permeability. Importantly, ALC dosing seems to be highly relevant in this process.

Conclusion: Results indicate that ALC improves and protects mitochondrial functional in a dose and time-dependent manner. While lower concentrations seem to be beneficial, higher concentration may interfere with cell bioenergetics in a negative way.

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