

## MITOCHONDRIAL FUNCTION AND ACETYL-L-CARNITINE NEUROPROTECTION

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**Background:** Mitochondrial dysfunction is involved in a number of chronic neurodegenerative disorders. Acetyl-L-carnitine (ALC) has been proposed to confer effective neuroprotection by increasing mitochondria viability, but little is known regarding the molecular mechanisms involved in its action.

**Aims:** Here, we propose to characterize the action of ALC in mitochondria bioenergetics and functional integrity. To achieve this goal we have exposed PC12 cells to the toxic effect of methamphetamine (METH 1 and 100  $\mu$ M) and pretreated cells with increasing doses of ALC (0.01, 0.1 and 1.0 mM). After either 24 or 72h of incubation, mitochondrial membrane integrity and mitochondrial mass were assessed by using, respectively, Mitotracker CMXRos (2  $\mu$ M) and Mitotracker Green (800 nM), and flow cytometry. Efficiency of glucose utilization was also assessed by incubating the cells with 37 kBq/mL of <sup>18</sup>F-FDG (2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose) in a low glucose serum-free medium for 60 minutes.

**Results:** Interestingly, although ALC by it self 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  $\mu$ M ( $p < 0.01$ ). 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 function 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.

**Relevance:** Understanding the role of ALC in mitochondrial function will be a key factor in formulating future therapeutic uses.

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