Neuroprotecting mechanisms of carnitine in mitochondrial dysfunction

Funding country: Portugal
Project starting year: 2010
Project ending year: 2013
Area(s) of research: Treatment responses, Mechanism of drug use and effects
Objectives:
The proposed project is expected to produce valuable knowledge-base for future ALC clinical therapies in drug-abuse related disorders. We expect to identify the pathways involved in the action of ALC using both in vivo and in vitro models of exposure to METH.

Scientific discipline(s) involved: Neurosciences, Pharmacology, Other medical sciences

Initial identified needs:
Acetyl-L-Carnitine (ALC) is a natural occurring compound that facilitates the transport of long chain free fatty acids across the mitochondrial membranes for β-oxidation. ALC has been proposed to have beneficial effects in chronic neurodegenerative disorders caused by production of abnormal proteins, mitochondrial dysfunction and oxidative stress, including long term drug-abuse. The main outcome of ALC supplementation is the improvement of mitochondrial function. ALC has been shown to be neuroprotective, in a dose and time dependent manner, through a variety of processes, including: membrane stabilization and ionic homeostasis, altered synaptic plasticity, increased expression of heme-oxygenase-1 (HO-1), heat shock proteins and superoxide dismutase, decreased expression of iNOS, increased resistance to neurotoxic events, and improved cognitive performance. Our group has successfully demonstrated that pre-treatment with ALC confers effective neuroprotection against 3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity, preventing mitochondrial oxidative damage, reducing carbonyl formation, decreasing mtDNA deletion, improving expression of respiratory chain components and, most importantly, preventing the typical MDMA-induced serotonin loss (Alves et al, Neuroscience, 2009). Taken together, these pre-clinical studies reinforce the beneficial potential of ALC as a neuroprotectant in neurodegenerative disorders. However, little is known about the molecular mechanisms underlying the action of ALC. We reason that ALC is likely to be a very valuable adjunct in clinical therapy for drug abuse related disorders and that elucidation of ALC molecular mechanisms underlying neuroprotection will be a fundamental step in formulating such therapies. Modified amphetamines are potent psychostimulant, well characterized and long used in our laboratory as models of neurotoxicity. Long-term exposure to these drugs results in high levels of neurotoxicity, mediated by oxidative stress and inflammation, which produces mitochondrial dysfunction and long-term damage to dopaminergic and serotonergic neurons. Particularly, the nigrostriatal damage evidenced after exposure to methamphetamine (METH) resembles the neurodegeneration observed in PD, making it a putative experimental model for the study of drug-induced neurodegenerative processes.

METH-induced activation of mitochondria-mediated intrinsic cell death signaling events is known to be associated with the loss of mitochondrial membrane potential, release of apoptogenic factors and subsequent activation of apoptotic cascades, creating a suitable model for exploring the action mechanisms of ALC. Therefore, we propose to investigate the molecular mechanisms involved in the neuroprotectant features of ALC, using exposure to METH as models of induced neurotoxicity in two different paradigms: 1) Exposure to METH of SH-SY5Y cell lines and neuronal primary cultures, aiming to understand, in a dose dependent study, the interaction of ALC with the ubiquitin-proteasome system (UPS) and autophagy. The proposed study will include investigating the role of ALC in the redox properties of the mitochondria, misfolding and aggregation of proteins and formation of inclusions-like bodies, as well as autophagic processes and altered fusion/fission regulation. 2) ALC was reported to increase the expression of Hsp 70 and heme- oxygenase-1 (decreasing also the expression of iNOS) indicating an association between the mechanisms of nitrosative stress and Hsp induction. Therefore, we are most interested in using the iNOS knock-out mice model to explore the role of ALC in METH-induced toxicity in low oxidative environment. Particular attention will be given to proteins involved in the maintenance of mitochondrial morphology and integrity. Likewise, the mechanisms regulating the NO-induced neurotoxicity will be a

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Published reference(s):