



**PERIPHERAL NEUROPATHIES: APOPTOSIS-PREVENTING ACTIVITY OF  
ACETYL-L-CARNITINE**

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The peripheral nervous system can be involved in a wide range of medical disorders with various pathophysiologicals. Autoimmune diseases, drug or toxin exposure, infection, metabolic insult or trauma can be the causes of peripheral neuropathies. Nerve damage may cause muscle weakness, altered functionalities and sensitivity, and chronic pain syndrome characterized by allodynia and hyperalgesia. Pathophysiological mechanisms related to neuropathic disease are associated with mitochondrial dysfunction that lead to the apoptotic cascade activation. Recently, Levine and coworker [1] have demonstrated that apoptotic phenomena are involved in the neuropathic pain-related behaviour hyperalgesia: in a rat model of neuropathy, induced by cancer or antiviral chemotherapy, the inhibition of caspases 1, 2, 3, 8, 9 reduced hyperalgesia.

Acetyl-L-Carnitine (ALCAR) is able to enhance pain threshold in acute conditions [2]. Moreover, ALCAR shows an anti-hyperalgesic effect in neuropathic pain syndrome induced by diabete, anticancer and antiretroviral treatment both in animal models and in human [3]. The existence of a link between apoptotic cell death and neuropathic pain encourages us to enquire the effect of ALCAR on apoptosis pathway. In a model of peripheral neuropathy, obtained by the loose ligation of the rat sciatic nerve (Chronic Constriction Injury; CCI), we describe a nerve apoptotic state that encompasses cytochrome C cytosolic release, activation of the cysteine protease caspase 3, and genome fragmentation. Treatment twice a day with Acetyl-L-Carnitine (ALCAR) 100 mg/kg i.p. but not with L-Carnitine 100 mg/kg i.p. or Gabapentin 70 mg/kg i.p. (equimolar dose to ALCAR), prevents apoptosis induction. ALCAR reduces cytosolic cytochrome C and caspase 3 active fragments (19 and 16 kDa) expression, evaluated by western blot, in a significative manner with respect to saline treatment. Accordingly, ALCAR treatment impairs caspase 3 Asp-Glu-Val-Asp (DEVD) – specific protease activity, as demonstrated by reduced levels of cleaved PARP (89 kDa). Finally, ALCAR decreases the number of piknotic nuclei, assessed by terminal deoxynucleotidyl-transferase-mediated dUTP nick-end labeling (TUNEL) technique. This protection correlates with the induction of the X-linked inhibitor of apoptosis protein (XIAP). Taken together these results show that CCI is a valuable model to enquire neuropathies-related apoptosis phenomena and that ALCAR is able to prevent regulated cell death in the damaged sciatic nerve, suggesting a neuroprotective profile.

[1] Joseph E.K., Levine J.D. (2004) *Eur. J. Neurosci.* 20: 2896-2902.

[2] Ghelardini C., Galeotti N., Calvani M., Mosconi L., Nicolai R., Bartolini A. (2002). *Neuropharmacology* 43: 1180-1187.

[3] Herzmann C., Johnson M.A., Youle M. (2005) *HIV Clin Trials* 66: 344-350.