

THE ROLE OF SIRT3 PATHWAY IN NEUROPATHIC PAIN AND OXIDATIVE STRESS

1)Ilari S. 2)Giancotti LA. 3)Lauro F. 4)Morabito C. 5)Malafoglia V. 6)Gliozzi M. 7)Tafani M. 8)Fini M. 9)Russo M. 10)Mollace V. 11)Salvemini D. 12)Muscoli C.

Free radicals plays a crucial role in the enhanced pain sensitivity experienced during several diseases. ROS accumulation modifies the activity of sirtuins, proteins that deacetylate histones and non-histone proteins playing an important role in regulation of inflammation and neurodegenerative diseases.

Sirtuin 3 is the major mitochondrial protein deacetylase. A recent proteomic survey reported that approximately 20% of mitochondrial proteins are acetylated, implicating SIRT3 as a key regulator of mitochondrial proteome function.

In the present study we evaluated the role of SIRT3 in the maintenance of basal levels of reactive oxygen species in a model of chronic constriction injury (CCI) of the sciatic nerve.

Animals were exposed to CCI of the sciatic nerve in the presence or absence of antioxidants. To demonstrate the involvement of SIRT3 modulation by free radicals products during CCI we detected the level of acetylation and activity of SIRT3 of mitochondrial compartment in spinal cord, and we demonstrated the post-translational modulation on cysteine residues of SIRT3 by HNE.

Our studies revealed that CCI leads to the development of hyperalgesia and allodynia. We reported that neuropathic pain induced by CCI is associated to SIRT3 inactivation in the spinal cord of CCI treated rats and this event seems to be related to mitochondrial protein hyperacetylation. These findings demonstrate for the first time that deactivation of sirtuins is involved in hyperalgesia and allodynia and that activation of SIRT3 by antioxidants is beneficial during oxidative stress induced by neuropathic pain.

This work has been supported by funds from PON03PE_00078_2, PON03PE_00078_1/F1, PON03PE_00078_2/F1.