THE ROLE OF MITOCHONDRIAL SIRT3IN NEUROPATHIC PAIN

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Summary: Neuropathic pain is one of the chronic painful and debilitating conditions which affects large population worldwide (7% to 18%) and disturbs the daily activities. The etiology and underlying mechanisms of such pains are poorly understood and several pharmacological and non-pharmacological approaches such as opioid analgesics, tricyclic antidepressants, anticonvulsants, local anesthetics, as well as acupuncture and electrical stimulation have been used to treat neuropathic pain. Nevertheless, these are not completely effective to relieve neuropathic pain, and novel options are thereby necessary to investigate. It was proven that reactive oxygen species and reactive nitrogen species (ROS and RNS) are implicated in the development and maintenance of chronic pain. In particular, the enhanced ROS production alters the mitochondrial genome and proteome through a number of mechanisms, including the accumulation of the lipid peroxidation 4-HNE, in pathologic quantities near lipid-rich cellular membranes. Approximately 20% of mitochondrial proteins are acetylated by SIRT3, a class III histone deacetylases (HDACs) protein. SIRT3is a mitochondrial protein, known to deacetylate histones and non-histone proteins and its activity can reduce ROS levels by directly modulating key antioxidant enzymes. SIRT3directly deacetylates the manganese-dependent superoxide dismutase (MnSOD), one of the primary mitochondrial antioxidant systems, significantly enhancing its ability to scavenge ROS.

Aim of investigation: In the present study we evaluated the role of SIRT3in the maintenance of basal levels of reactive oxygen species in a model of chronic constriction injury (CCI) of the sciatic nerve.

Methods: To evaluate whether free radicals products contributes to the development of hyperalgesia following post-operative pain by a protein carbonylation, the animals will be exposed to chronic constrictive injury (CCI) to the sciatic nerve of the right hind paw. Animals received continuous infusion of natural antioxidants by mini-pump for 21days Hyperalgesia and allodynia were measured at different time points by Plantar test, Randall-Selitto and Von Frey filaments in order to dissect the type of pain and the protective role of our pharmacological tools. At the end of the experiments animals were sacrificed and spinal cord tissue extract and stored for further analysis. To demonstrate the involvement of SIRT3modulation by free radicals products during CCI we detected the level of acetylation and activity of SIRT3of mitochondrial compartment in spinal cord, and we demonstrated the post-translational modulation on cysteine residues of SIRT3by HNE.

Results: Our studies revealed that CCI leads to a time-dipendent development of hyperalgesia and allodynia. We reported that neuropathic pain induced by CCI is associated to SIRT3inactivation in the spinal cord of CCI treated rats and this event seems to be related to mitochondrial protein hyperacetylation. Removal of free radicals by antioxidants during neuropathic pain exerts anti-hyperalgesic effect together with inibition to hyperacetylation, lipid peroxidation and enhanced SIRT3activity.
Conclusion: These findings demonstrate that deactivation of sirtuins is involved in hyperalgesia and allodynia and that activation of SIRT3by antioxidants is beneficial during oxidative stress induced by neuropathic pain.