NAD+ dependent SIRT1 deacetylase and acute inflammatory pain: the crucial role of oxidative stress modulation.

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Sirtuins, the class III histone deacetylases (HDACs), are widely distributed and have been shown to regulate a variety of physiopathological processes, such as inflammation, metabolism and cell cycle regulation. Sirtuins catalize the deacetylation of the e-amino group of lysine residues of histones and non-histone proteins and are involved in regulating transcriptional activity and protein function. The best characterized sirtuins is SIRT1, a nuclear protein reported to regulate critical metabolic and physiological processes. SIRT1 either directly or indirectly can influence the redox property of the cell and it is also regulated by oxidative stress. SIRT1 activation confers protection against myocardial infarction and ischemia/reperfusion injury in the heart.

In the last years, considerable evidence demonstrates the central role of reactive oxygen species and reactive nitrogen species (ROS and RNS) in inflammation and subsequent development of inflammatory pain. Superoxide is implicated in the development and maintenance of hyperalgesia; it stimulates the roduction of cytokines and contributes to the formation of the peroxynitrite (PN) and lipid peroxidation products.

To evaluate whether free radicals products such as PN and HNE contributes to the development of hyperalgesia following acute pain by a protein tyrosine nitration and protein carbonylation, the animals were exposed to intraplantar carrageenan administration in the presence or absence of antioxidants. At the end of the experiments animals were sacrificed and paw or spinal cord tissue extract and stored for further analysis. To demonstrate the involvement of SIRT1 modulation by free radicals products during hyperalgesic state in a models of carrageenan we detected the level of acetylation and S-Nitrosylation of nuclear compartment in spinal cord neuron. Furthermore, we evaluated the modulation of SIRT1 expression and its activity to verify our hypothesis. We demonstrated the post-translational modulation on cysteine residues of SIRT1 by HNE.

Our studies revealed that intraplantar injection of carrageenan leads to a time-dependent development of hyperalgesia and inflammation.

We reported that inflammatory pain is associated to SIRT1 inactivation in the spinal cord of carrageenan treated rats and this event seems to be related to nuclear protein hyperacetylation and s-nitrosylation. Removal of free radicals by antioxidant during acute inflammation exerts anti-hyperalgesic effect together with inhibition of hyperacetylation, nitrosylation, lipid peroxidation, PGE_2 and cytokines release, and enhanced SIRT1 activity.

These findings are innovative since virtually nothing is known on the roles of post-translational modulation due to acetylation/deacetylation in pain. The development of new therapeutic scheme would allow the inhibition of free radicals post-translational modulation by regulation of intra-and intercellular signals transmission without directing blocking involved neurotransmitters action. The activation of SIRT1 by polyphenols would be a new target in therapeutic intervention for the management of pain.

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