Protective effects of antioxidants during acute inflammatory pain: the role NAD^+-dependent SIRT1 deacetylase

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Generation of free radicals plays a crucial role in the enhanced pain sensitivity experienced during inflammatory diseases. Superoxide is implicated in the development and maintenance of hyperalgesia; it stimulates the production of cytokines, causes single-strand DNA damage and poly-ADP-ribose-polymerase (PARP) activation and contributes to the formation of the peroxynitrite (PN) and lipid peroxidation products. Sirtuin 1 (SIRT1) deacetylates histones and non-histone proteins including transcription factors, thereby playing an important role in regulation of diabetes, inflammation, neurodegenerative and cardiovascular diseases. Although the inhibition of SIRT1 by PARP1 activation has been determined in response to H_2O_2-induced cell senescence, the effect of oxidative/genotoxic stimuli on PARP1 activation and SIRT1 activity still remains to be shown. 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. Here we show that removal of free radicals by $FeTMPyP^{5+}$, a PN decomposition catalyst, or by a natural antioxidant, is able to block the thermal hyperalgesia in the carrageenan-induced inflammation. This effect was associated with inhibition of edema, PGE_2 and cytokines release, lipid peroxidation and nitrotyrosine formation in the paw exudates and to nitrotyrosine formation at the level of the spinal cord. We report that SIRT1 activity is decreased in the spinal cord of carrageenan treated rats. Removal of free radicals by antioxidant during acute inflammation exerts anti-hyperalgesic effect together with inhibition of nitration, lipid peroxidation, PGE_2 and cytokines release, and enhanced SIRT1 activity. These findings demonstrate for the first time that activation of SIRT1 by antioxidants is beneficial during oxidative stress induced hyperalgesia and inflammation. Hence, the activation of SIRT1 by polyphenols would be a new target in therapeutic intervention for the management of pain suffering patients.

This work has been supported by funds from PON03PE_00078_1, PON03PE_00078_2 and GR-2010-2318370.