The role for NAD$^+$-dependent SIRT3 deacetylase during opioid tolerance: a new therapeutic approach for natural antioxidants

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Opiate analgesic morphine is the mainstay of pain management in conditions ranging from acute to chronic pain and is used over prolonged periods. Though, their clinical utility is nearly always hampered by the development of analgesic tolerance as well as painful hypersensitivity known now as paradoxically morphine-induced hyperalgesia. Considerable evidence implicates superoxide ($\bullet O_2^-$) and peroxynitrite ($ONOO^-$) in the development of these opiate-induced side effects and demonstrate that pharmacologic inhibition of $\bullet O_2^-$ and $ONOO^-$ can prevent and reverse the characteristic pathologies associated with morphine-induced hyperalgesia and tolerance as alterations in glutamatergic neurotransmission and neuroinflammation.

Sirtuins (SIRT1-SIRT7), the class III histone deacetylases (HDACs), are widely distributed and have been shown to regulate a variety of physiopathological processes, such as inflammation, cellular senescence, differentiation, metabolism and cell cycle regulation. The best characterized sirtuins are SIRT1,a nuclear protein reported to regulate critical metabolic and physiological processes, and SIRT3, the major mitochondrial protein deacetylase.

Targets of SIRT3 deacetylation are widespread and are implicated in a host of cellular pathways, including oxidative phosphorylation, fatty acid metabolism, oxidative stress response, and alcohol metabolism. Recent data suggest that SIRT1 are target of protein nitration in a model of chronic obstructed pulmonary disease in human lung tissue and given the sequence homology among the sirtuin family of proteins, it is likely that SIRT3 is also susceptible to protein nitration.

Naturally occurring dietary polyphenols, such as resveratrol, curcumin, quercetin, and catechins, have antioxidant and anti-inflammatory properties and have also been shown to activate sirtuins directly or indirectly in a variety of models. Therefore, modulation of glutamatergic transmission and activation of SIRT3 by polyphenols could be beneficial in therapeutic intervention of chronic pain and for the modulation of hyperalgesia observed during opioid tolerance.

Our aim is to generate data on role of post-translational modifications of oxidative stress-mediated sirtuins during morphine induced hyperalgesia and tolerance.

Results of our studies revealed that repeated doses of morphine in mice develop antinociceptive tolerance associated with superoxide production and that co-administration of morphine with an antioxidant inhibit these effects. In addition, we demonstrated the involvement of the mitochondrial SIRT3 and MnSOD modulation by free radicals products during opioid tolerance and identified new classes of natural antioxidant drugs able to reinstate the activities of SIRT3 and endogenous antioxidant system inactivated during the development of opioid tolerance. Antioxidant employment prevents nitration and inactivation of MnSOD and SIRT3 and overall inhibits hyperalgesia occurring during opioid tolerance.

Results of our study support the hypothesis that free radicals post-translational modulation of key proteins involved in the regulation of protein acetylation pathway is an important pathway used by superoxide/peroxynitrite to mediate the development and maintenance of opioid induced hyperalgesia and indicate the importance of the development of new therapeutic approach to counteract the side effects of prolonged opioid use.

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