S-nitrosoglutathione reductase (GSNOR) deficiency-induced *S*-nitrosylation results inspontaneous pain response

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Peroxynitrite and its reactive precursors superoxide and nitric oxide are critically important in the development of pain of several etiologies. Recently, it has been demonstrated that free radicals production is involved in pain development and maintenance *via* post-translational modulation due too tyrosine nitrations. Pharmacologic scavenging of superoxide and nitric oxide, by preventing tyrosine nitrations, inhibits inflammatory and neuropathic pain, as well as morphine-induced hyperalgesia and tolerance.

Besides the generation of the reactive nitrogen species, nitric oxide can also react with protein cysteine residues (*S*-nitrosylation). This redox modification of proteins represents an important post-translational modification that transduces nitric oxide-dependent signals throughout the cell more efficiently, and reversibly. However, despite the well-known implication of nitric oxide in pathophysiology, the specific role of *S*-nitrosothiols (SNOs) formation during pain response remains to be identified.

S-nitrosoglutathione reductase (GSNOR) is an evolutionary conserved and widely expressed enzyme that, by reducing the low-molecular weight nitrosothiol *S*-nitrosogluthione (GSNO), decreases indirectly the concentration of protein SNOs.

In order to determine the potential role of *S*-nitrosylation in pain pathway, we employed GSNOR-null (GSNOR-KO) mice, which maintain the capability to produce nitric oxide, but are unable to reduce SNOs. Here we show, for the first time, that GSNOR-KO mice develop spontaneous mechanical allodynia and thermal hyperalgesia measured by using von Frey filaments and Plantar Test respectively. We also demonstrate that mechanical allodynia and thermal hyperalgesia are associated with protein *S*-nitrosilation in the dorsal horn of lumbar spinal cord sections and that antioxidant administration is able to block these events.

These findings provide, for the first time, a crucial evidence of the role of *S*-nitrosylation in pain. These findings could provide novel insight into the involvement of GSNOR and *S*-nitrosylation in pain identifying a new target for the development of pain therapies.

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