ACTIVATION OF PPARγ AS A NEW PHARMACOLOGICAL STRATEGY TO TREAT NEUROPATHIC PAIN

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Neuropathic pain (NP) is a chronic pain caused by a primary lesion or dysfunction of the somatosensory nervous system, associated with maladaptive neuronal plasticity phenomena (Treede et al., 2008).

Recent preclinical evidence suggests that neuroinflammatory processes, characterized by infiltration of immunocompetent cells and activation of glial cells both in the peripheral and central nervous system, contribute to the development and maintenance of NP. Thus, the molecular pathways involved in neuroinflammation offer a pharmacological target for the development of effective therapies for the treatment of NP and related disorders.

The peroxisome proliferator receptors (PPAR) are a group of nuclear receptor proteins that function as transcription factors, regulating the expression of genes. There are three isoforms α, β/δ and γ. The PPARγ isoform is localized in adipocytes, intestinal cells, macrophages and is also widely expressed in the central nervous system, both at the neuronal and at the glial levels (Tureyen et al., 2007; Xing et al., 2007). It controls the expression of genes involved in the regulation of lipid metabolism and neuroinflammation (Landreth et al., 2001; Kapadia et al., 2008).

Converging evidence suggests an important neuroprotective and anti-inflammatory role of PPARγ in the central nervous system, where it regulates glial activation through the inhibition of NF-kB transcription factor and production of pro-inflammatory cytokines (Tureyen et al., 2007; Xing et al., 2007).

This study investigates the therapeutic potential of the PPARγ agonist pioglitazone given during the development of NP. Chronic pain was induced in male Wistar rats using the Spinal Nerve Ligation (SNL) model that consists in the ligation of L5 spinal nerve. Sham operated animals were used as a control. The effects of chronic administration of pioglitazone on tactile allodynia and on emotional and cognitive dysfunction (anxiety and memory) associated with NP were evaluated.

The results demonstrate that, in animals subjected to SNL, treatment with pioglitazone significantly reduces mechanical allodynia scored by von Frey test, anxiety scored by elevated plus maze test and the impairment in short-term recognition memory scored by novel object recognition test. Our findings indicate that the anti-inflammatory action of pioglitazone may be responsible for the reduction of the sensory component of NP, but also for the reduction of the affective and cognitive symptoms associated with this condition.

Altogether, these experiments suggest that pioglitazone may be a promising therapeutic strategy for the treatment of NP since it is able to attenuate not only allodynia but also to mitigate the negative affective and cognitive symptoms associated with NP.

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