

Combined treatment with Propentofylline and IL-4 alleviates central neuropathic pain in male spinal cord injured rats by suppressing P38 MAP kinase activation

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Abstract

The development of central Neuropathic Pain (CNP) occurs in 40-50% of patients with spinal cord injury (SCI). Microglial cell activation plays a central role in neuroinflammation associated with CNP development and persistence after SCI. The current study builds upon prior work from the laboratory that has demonstrated the therapeutic effects of acute xanthine derivative Propentofylline (PPF) administration, independently or with the anti-inflammatory cytokine Interleukin-4 (IL-4), in promoting the conversion of activated microglia from a pro- to anti-inflammatory phenotype. This conversion was accompanied by a reduction in the development and severity of CNP across genders in rodent SCI that was more pronounced in males.

Here the gender disparity in the therapeutic response to PPF+IL-4 was further explored by immunohistopathological assessment. For this work the dorsal horn of the L4-L5 spinal cord from injured animals across the different treatment and control cohorts was probed to determine if a correlation existed between specific proteins implicated in CNP and gender-dependent behavioral pain outcomes. It was identified that the phosphorylation of the P38 MAP kinase (pP38 MAPK [Thr180/Tyr182]), a known pain-potentiating kinase, was reduced in microglia of spinal cord injured male rats following PPF+IL-4 treatment. A significant correlation was found between the treatment-induced reduction in microglial P38 activation and improved sensory outcomes. These findings identify PPF+IL-4 as a potential combined therapeutic approach to perturb SCI-induced CNP that acts putatively through reducing the phosphorylation of the pain-inducing MAPK kinase P38.