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Molecular evidence for the involvement of PPAR-δ and PPAR-γ in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma.

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Abstract

BACKGROUND: Palmitoylethanolamide (PEA) is an endogenous fatty acid amide displaying anti-inflammatory and analgesic actions. Moreover, several data have suggested that PEA reduced inflammation and tissue injury associated with spinal cord trauma and showed a regulatory role for peroxisome proliferator-activated receptor (PPAR)-α signaling in the neuroprotective effect of PEA. However, several other mechanisms could explain the anti-inflammatory and anti-hyperalgesic effects of PEA, including the activation of PPAR-δ and PPAR-γ. The aim of the present study was to carefully investigate the exact contribution of PPAR-δ and PPAR-γ in addition to PPAR-α, in the protective effect of PEA on secondary inflammatory damage associated with an experimental model of spinal cord injury (SCI).

METHODS: SCI was induced in mice through a spinal cord compression by the application of vascular clips (force of 24 g) to the dura via a four-level T5 to T8 laminectomy, and PEA (10 mg/kg, intraperitoneally, 1 and 6 hours after SCI) was injected into wildtype mice and into mice lacking PPAR-α (PPAR-αKO). To deepen the ability of specific PPAR-δ and PPAR-γ antagonists to reverse the effect of PEA, mice were administered GSK0660 or GW9662, 30 minutes before PEA injection.

RESULTS: Genetic ablation of PPAR-α in mice exacerbated spinal cord damage, while PEA-induced neuroprotection seemed be abolished in PPARαKO mice. Twenty-four hours after spinal cord damage, immunohistological and biochemical studies were performed on spinal cord tissue. Our results indicate that PPAR-δ and PPAR-γ also mediated the protection induced by PEA. In particular, PEA was less effective in PPAR-αKO, GSK0660-treated or GW9662-pretreated mice, as evaluated by the degree of spinal cord inflammation

and tissue injury, neutrophil infiltration, proinflammmatory cytokine, inducible nitric oxide synthase expression and motor function. PEA is also able to restore PPAR-δ and PPAR-γ expression in spinal cord tissue.

CONCLUSION: This study indicates that PPAR-δ and PPAR-γ can also contribute to the anti-inflammatory activity of PEA in SCI.

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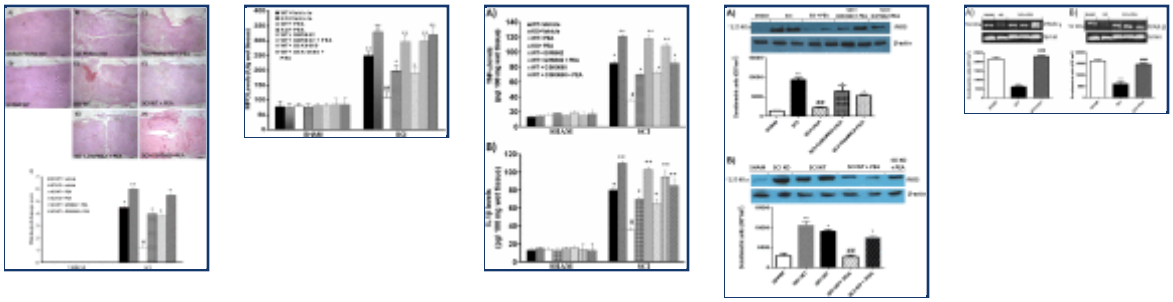

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