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INHIBITION OF TLR4/MyD88/TAK1/NF-κB/COX-2 PATHWAY ACTIVATION CONTRIBUTES TO PROTECTIVE EFFECT OF BEXAROTENE, A RXR AGONIST, AGAINST LIPOPOLYSACCHARIDE-INDUCED INFLAMMATORY HYPERALGESIA

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Bacterial LPS causes inflammation leading to decreased pain threshold or increased pain sensitivity termed as hyperalgesia. The aim of this study was to determine effect of a selective RXR agonist, bexarotene, on TLR4/MyD88/TAK1/NF-κB/COX-2 signaling pathway in relation to proinflammatory cytokine expression in the central nervous system in LPS-induced hyperalgesia in mice. Male Balb/c mice were divided into 8 groups: (1) saline, (2) LPS, (3) DMSO, (4) LPS+bexarotene (0.1 mg/kg), (5) LPS+bexarotene (1 mg/kg), (6) LPS+bexarotene (3 mg/kg), (7) saline+bexarotene (10 mg/kg), and (8) LPS+bexarotene (10 mg/kg). DMSO (1%; 4 ml/kg) or bexarotene (10 mg/kg) were injected simultaneously with saline (10 ml/kg) or LPS (10 mg/kg). Following determination of reaction time to thermal stimuli within 30 s 6 h after injection, the mice were euthanized. Brains and spinal cords were collected from the animals. Tissue homogenates were used for the measurement of TLR4, MyD88, TAK1, phosphorylated TAK1, NF-κB p65, phosphorylated NF-κB p65, COX-2, IL-1β, RXRα, and β-tubulin protein expression by using immunoblotting method and COX-2 activity in addition to PGE_2 levels by using suitable enzyme-linked immunosorbent assay kits. LPS caused a decrease in hot plate latency compared to saline-treated group. Bexarotene at 10 mg/kg dose prevented the LPS-induced hyperalgesia 6 h after drug injection. Decreased RXRα protein expression was associated with increased expression of TLR4, MyD88, phosphorylated TAK1, NF-κB p65, phosphorylated NF-κB p65, COX-2, and IL-1β proteins as well as COX-2 activity and PGE_2 levels in the tissues of LPS-treated mice. The LPS-induced changes were prevented by bexarotene. DMSO or bexarotene had no effect on the hot plate latency in saline-treated mice. These findings suggest that decreased activity of TLR4/MyD88/TAK1/NF-κB/COX-2 pathway associated with proinflammatory cytokine expression contributes to the effect of bexarotene to prevent LPS-induced hyperalgesia in mice. This work was financially supported by Mersin University (2018-1-TP3-2814) and The Scientific and Technological Research Council of Turkey (SBAG-217S235).