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ORIGINAL ARTICLE

Pharmacological studies on the anti-inflammatory and immunomodulatory role of Pentoxifylline and its interaction with nitric oxide (NO) in experimental arthritis in rats

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Abstract
Aim Present study was designed to evaluate protective effects of Pentoxifylline and its potentiation with low dose of nitric oxide (NO) modulators in adjuvant-induced experimental arthritis in rats.
Method Wistar rats (200–300 g, $n = 8$ per group) of both sexes were used in the study. On day "0" experimental arthritis was induced by injecting 0.2 ml of Complete Freund's adjuvant (CFA) in sub-planter region of right hind paw of animals. Pentoxifylline treatment alone and in combination with NO modulators was given (i.p.) from day 14 to 28. Various arthritic parameters were recorded and blood and joint synovial fluid was collected for biochemical analysis.
Results CFA inoculation significantly increases (1) arthritic index (2) ankle diameter (3) paw volume (4) histopathology score (5) serum TNF-α, IL-6, IL-1β and synovial TNF-α levels ($p < 0.001$) (6) serum Th_1 and Th_2 cytokine levels g) MDA levels in rat paw tissue homogenates (7) serum NF-κB levels. Significant decrease in serum IL-10 levels and SOD activity was observed in rats after CFA inoculation. Decrease in body weight and suppressed general quality of life of CFA inoculated rats was also observed. These CFA-induced arthritic changes were significantly reversed by Pentoxifylline alone and in combination with low dose of NO modulators ($p < 0.05$).
Conclusion These results are suggestive of protective effects of Pentoxifylline and its potentiation in combination with low dose of NO modulators. These results may provide new pharmacological therapy for management of rheumatoid arthritis (RA).

Keywords Pentoxifylline · Nitric oxide · Cytokines · NF-κB · Arthritic index · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disorder; however, its etiology is still largely unknown. It is a lifelong progressive disorder with significant morbidity and premature mortality. Fibroblasts and chondrocytes along with both innate and adaptive immune system, play an important role in development and progression of RA (van der Woude and Huizinga 2008). Some recent studies have reported that, cytokine IL-18 along with TNF-α is responsible for the progression of RA (Theill et al. 2002; Cadena et al. 2003).

Endogenously produced nitric oxide (NO) plays a crucial role in signaling of inflammatory pathways and is also involved in many physiological/pathological processes. Depending on environmental and patho-physiological conditions, NO can produce totally opposite biological effects (Li and Wan 2013; Pal et al. 2006, 2009). Role of free radicals have been evaluated in stress-induced immunological changes and established elevated oxidative markers may be responsible for suppressed immune cell functions (Pal et al. 2011, 2016a, b). Destruction of inflamed joints within the synovia occurs due to auto-immune disorder produced by oxidative stress (Vasanthi et al. 2009). Free radicals generated by NO and oxygen

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