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Protective Effect of Bexarotene, a Selective RXRα Agonist, against Hypotension Associated with Inflammation and Tissue Injury Linked to Decreased Circulating iNOS Levels in A Rat Model of Septic Shock

Authors : Bahar Tunctan, Sefika Pinar Kucukkavruk, Meryem Temiz-Resitoglu, Demet Sinem Guden, Ayse Nihal Sari, Seyhan Sahan-Firat

Abstract : We hypothesized that rexinoids such as bexarotene, a selective retinoid X receptor α (RXRα) agonist, may be beneficial for preventing mortality due to inflammation associated with increased expression/activity of inducible nitric oxide synthase (iNOS) induced by lipopolysaccharide (LPS). Therefore, we investigated effects of bexarotene on the changes in circulating protein levels of iNOS (an index for systemic iNOS expression), myeloperoxidase (MPO) (an index for systemic inflammation), and lactate dehydrogenase (LDH) (an index for systemic tissue injury) in LPS-induced systemic inflammation model resulting in septic shock in rats. Rats were injected with saline (4 ml/kg; i.p.), LPS (10 mg/kg; i.p.), dimethylsulphoxide (4 ml/kg, 0.1%; s.c.) at time 0. Mean arterial blood pressure and heart rate were measured using a tail-cuff device. Bexarotene (0.03, 0.1, 0.3, and 1 mg/kg; s.c.) was administered to separate groups of rats 1 h after injection of saline or LPS. The rats were sacrificed 4 h after saline or LPS injection and blood was collected for measurement of serum iNOS, MPO, and LDH protein levels. Blood pressure decreased by 31 mmHg and heart rate increased by 63 bpm in the LPS-treated rats. Bexarotene at 0.3 and 1 mg/kg doses caused 20% mortality 4 h after LPS injection. In the LPS-treated rats, serum iNOS, MPO, and LDH protein levels were increased. Bexarotene only at 0.1 mg/kg dose prevented the LPS-induced hypotension and increased in iNOS, MPO, and LDH protein levels. These data are consistent with the view that a decrease in systemic iNOS levels contributes to the beneficial effect of bexarotene to prevent the hypotension associated with inflammation and tissue injury during rat endotoxemia. [This work was financially supported by The Scientific and Technological Research Council of Turkey (SBAG-109S121)].

Keywords : bexarotene, inflammation, iNOS, lipopolisaccharide, RXRa
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