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New insights into the role of pioglitazone in murine sepsis model by cecal ligation and puncture: the role of nitrergic system and TNF-α

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Background and Aims: Sepsis and sepsis-related organ failure remain as major challenges for scientists. Structural components of microorganisms, initiate a cascade of events leading to the production of numerous endogenous proinflammatory mediators such as cytokines, tumor necrosis factor-α (TNF-α) and nitric oxide (NO). Several in vitro studies demonstrated that activation of peroxisome proliferator-activated receptor-γ (PPARγ) via thiazolidinediones (e.g., pioglitazone) exhibits anti-inflammatory effects. This study was designed to evaluate the role of pioglitazone in high-grade septic mice survival, focus on TNF-α and nitrergic system involvement.
Methods: Diffused sepsis was induced by cecal ligation and puncture (CLP) surgery in male Swiss mice (23-29 g). CLP was performed through ligation below the ileocecal valve after midline laparotomy, followed by needle puncture of the cecum, resulting in translocation of enteric bacteria into the blood. Pioglitazone (5, 10 and 20 mg/kg) was administered by gavage daily for 5 days prior to surgery. After CLP, mortality was observed within 3 days. NO involvement was assessed by chronic administration of a non-selective NO synthase (NOS) inhibitor, L-NG-Nitroarginine methyl ester (L-NAME). Plasma levels of TNF-α were measured by mouse TNF-α enzyme-linked immunosorbent assay (ELISA) kit.
Results: Pioglitazone (20 mg/kg) significantly improved survival in high grade septic mice ($p < 0.001$). The chronic intraperitoneally co-administration of L-NAME (0.1 and 0.5 mg/kg, daily) with a daily non-effective dose of pioglitazone, 5 mg/kg, significantly increased survival ($p < 0.001$). TNF-α plasma levels in treated mice with effective dose of pioglitazone (20 mg/kg) were in lower concentrations by comparison with control group.
Conclusions: CLP is currently considered as the gold standard in sepsis research. The present study demonstrated for the first time that pioglitazone can improve survival in mouse sepsis model by CLP, which is accompanied by a reduction in inflammatory mediators.

Keywords: Sepsis; Pioglitazone; Nitric oxide; Tumor necrosis factor-α