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Pioglitazone Ameliorates Methotrexate-Induced Renal Endothelial Dysfunction via Amending Detrimental Changes in Antioxidant Profile, Systemic Cytokines and Apoptotic Factors

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Abstract : Methotrexate (MTX) is widely used in treatment of cancers and autoimmune diseases. However, nephrotoxicity is one of the most important side effects of MTX. The peroxisome proliferator-activated receptor gamma agonist, pioglitazone (PIO), is known to exert anti-inflammatory and reno-protective effects in various kidney injuries. The purpose of this study was to investigate the potential involvement of endothelial damage in MTX-induced renal injury and to elaborate the possible protective effect of PIO against MTX-induced nephropathy. Compared with saline-treated rats, treatment with MTX (7 mg/kg for 3 day) caused significant elevations in serum levels of urea and creatinine, increased renal nitrate/nitrite level and impaired renovascular responsiveness of isolated perfused kidney to endothelium-dependent vasodilations induced by acetylcholine (0.01-2.43 nmol) and isoprenaline (1µmol). These effects were abolished by concurrent treatment with PIO (2.5 mg/kg, for 5 days starting two days before MTX). Alternatively, MTX treatment did not affect endothelium-independent renovascular relaxation induced by sodium nitroprusside (1-30 µmole). The possibility that alterations in renal antioxidants, circulating cytokine and apoptotic factor (Fas) levels contributed to MTX-PIO interaction was assessed. PIO treatment abrogated renal oxidative stress (decreased reduced glutathione and catalase activity and increased malondialdehyde), elevated serum cytokine (interleukin-6, interleukin-10, tumor necrosis factor-alpha and transforming growth factor-beta1) and Fas induced by MTX. Histologically, MTX caused defused tubular cells swelling and vacuolization associated with endothelial damage in renal arterioles. These effects disappeared upon co-treated with PIO. Collectively, PIO abolished MTX-induced endothelium dysfunction and nephrotoxicity via ameliorating oxidative stress and rectifying cytokines and Fas abnormalities caused by MTX.

Keywords : methotrexate, pioglitazone, endothelium, kidney
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