Amelioration of lipopolysaccharide-induced acute kidney injury by simvastatin: Involvement of mitochondrial apoptotic and NF-κB signaling pathways

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Background: Sepsis remains the most important cause of acute kidney injury (AKI) and is an predictor of poor outcome. Lipopolysaccharide (LPS) model of experimental sepsis reproduces most of the clinical features, including AKI associated with inflammatory damage and apoptosis. Statins have confirmed anti-inflammatory and anti-apoptotic effects in different inflamed tissues.

Aim: This study evaluated potential underlying mechanisms of simvastatin reno-protective effects through the modulation of apoptotic pathway in LPS-induced AKI.

Methods: Male Wistar rats were divided into control (saline), LPS (0.25 of the medial lethal dose of LPS), simvastatin group (10, 20 or 40 mg/kg per group). Simvastatin was given orally as a five-day pre-treatment prior to a single dose of LPS, and 48 afterwards the animals were sacrificed. Renal tissue inflammatory damage was assessed by histopathological examination (haematoxylin-eosin staining), and expressed as a tissue damaged score (TDS). Apoptosis was analysed by TUNEL (DNA fragmentation assay) and expressed as an apoptotic index (AI), and immunohistochemically by detection of cleaved caspase-3, cytochrome C, Bcl-XL, inhibitor of apoptosis-survivin as well as expression of nuclear factor (NF)-κB. The number of immunopositive epithelial cells was expressed as a percentage of positive stained cells in tissue sections/total number of cells × 100.

Results: Simvastatin+LPS treatment in dose dependent manner ameliorated histopathological injury expressed as TDS vs. LPS (2.45±0.12 and 1.3±0.5 in simvastatin 20 mg/kg and 40 mg/kg vs 3.58±0.48, p<0.01, respectively). Results showed that LPS induced extensive renal tubular apoptosis trough overexpression of cytochrome C (64.6%±10.8) and cleaved caspase-3 (48.7%±12.3), indicating involvement of mitochondrial apoptosis pathway and AI (38.7%±6.2). The most significant anti-apoptotic effect demonstrated simvastatin 40 mg/kg vs LPS by decrease AI (p<0.05), caspase-3 (p<0.01) and cytochrome C (p<0.05) expression. Simvastatin 40 mg/kg stimulated anti-apoptotic Bcl-XL (72.7% ± 21.4) (vs. LPS, p <0.01) and cell survival marker-survivin (determined as cytoplasmic staining) expression. Simvastatin also activates and up-regulate NF-κB (distinct brown nuclear staining) in renal tubular cells that showed strong positive correlation with survivin (r=61501;0.82), indicating potential anti-apoptotic mechanism of simvastatin in AKI.

Conclusion: Simvastatin ameliorates LPC induced renal injury and involves an anti-apoptotic effect through the regulation of the mitochondrial apoptotic and up-regulating survivin/NF-κB pathways.