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Short communication

The PPAR-γ ligand 15-deoxy$^{\Delta 12,14}$ prostaglandin J_2 reduces the liver injury in endotoxic shock

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Abstract

We demonstrate here for the first time that the endogenous cyclopentenone prostaglandin 15-deoxy-$^{\Delta 12,14}$-prostaglandin J_2 (15*d*-prostaglandin J_2) reduces the liver injury (rise in serum transaminases) caused by severe endotoxaemia (6 mg/kg *Escherichia coli* endotoxin i.v. for 6 h) in the anaesthetised rat. The protection of the liver afforded by this potent agonist of PPAR-γ was not secondary to a haemodynamic effect. Thus, 15*d*-prostaglandin J_2 and other PPAR-γ agonists may be useful in the therapy of septic shock.

Keywords: Shock; PPAR; 15-Deoxy$^{\Delta 12,14}$ prostaglandin J_2

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand-activated transcription factors that are related to retinoid, steroid, and thyroid hormone receptors. The PPAR-γ receptor subtype seems to play a pivotal role in the regulation of cellular proliferation and inflammation. Recent evidence also suggests that the cyclopentenone prostaglandin 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15*d*-prostaglandin J_2), which is a metabolite of prostaglandin D_2, functions as an endogenous ligand for PPAR-γ. 15*d*-Prostaglandin J_2 attenuates the activation of the transcription factor nuclear factor kappa B (NF-κB) by preventing the phosphorylation of its inhibitor protein by IK kinase (Rossi et al., 2000). It is now widely accepted that 15*d*-prostaglandin J_2 attenuates the NF-κB-mediated transcriptional activation of many pro-inflammatory genes by PPAR-γ-dependent and PPAR-γ-independent mechanisms (Straus and Glass, 2001). We have recently discovered that 15*d*-prostaglandin J_2 reduces the tissue injury caused by ischaemia–reperfusion injury of the heart (Wayman et al., 2002) and by acute and chronic inflammation (Cuzzocrea et al., 2002). Here, we report for the first time that 15*d*-prostaglandin J_2 also attenuates the liver injury caused by endotoxic shock in the rat.

Male Wistar rats were anaesthetized with thiopentone sodium (120 mg/kg i.p.) and received an injection of endotoxin (6 mg/kg i.v., *Escherichia coli*, serotype 0127:B8). All rats were instrumented for the measurement of systemic haemodynamics. A blood sample was taken at 6 h after injection of endotoxin in order to determine the serum levels of the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Rats were treated with either 15*d*-prostaglandin J_2 (0.3 mg/kg i.v. at 30 min prior to endotoxin) or its vehicle (10% dimethyl sulfoxide). Data were analysed by one-way (or two-way) analysis of variance (ANOVA) followed by a Dunnett's post hoc test for multiple comparisons.

Injection of endotoxin caused a fall in mean arterial blood pressure from 135 ± 5 to 96 ± 4 mm Hg at 6 h ($P<0.05$). Endotoxaemia for 6 h also resulted in a significant increase in the serum levels of aspartate aminotransferase and alanine aminotransferase indicating the development of liver injury (Fig. 1). Most notably, pretreatment of rats with the PPAR-γ agonist 15*d*-prostaglandin J_2 abolished the liver injury, but did not affect the hypotension caused by endotoxin in the rat (91 ± 6 mm Hg at 6 h).

Thus, this study demonstrates that 15*d*-prostaglandin J_2 reduces the liver injury associated with endotoxic shock in the rat. What then is the mechanism by which this cyclopentenone prostaglandin exerts beneficial effects against the organ injury in endotoxic shock? 15*d*-Prostaglandin J_2 is a

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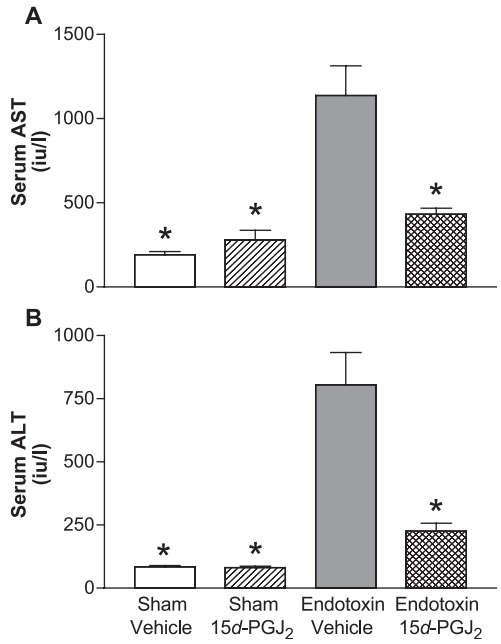

Fig. 1. Alterations in the serum levels of (A) aspartate aminotransferase (AST) and (B) alanine aminotransferase (ALT) in rats subjected to the surgical procedure and pretreated with either 10% dimethyl sulfoxide (Sham Vehicle Group, $n=11$) or 15*d*-prostaglandin J_2 (Sham 15*d*-PGJ_2 Group, $n=4$). Rats subjected to endotoxic shock (Endotoxin, 6 mg/kg i.v.) were pretreated with either 10% dimethyl sulfoxide (Endotoxin Vehicle Group, $n=11$), or 15*d*-prostaglandin J_2 (Endotoxin 15*d*-PGJ_2 Group, $n=7$). Note that endotoxemia caused a significant increase in the serum levels of aspartate aminotransferase and alanine aminotransferase, which was attenuated by 15*d*-prostaglandin J_2. $^*P<0.05$ when compared with Endotoxin Vehicle Group by ANOVA followed by Dunnett's post hoc test.

potent agonist of PPAR-γ and various chemically distinct agonists of PPAR-γ attenuate the activation of macrophages caused by endotoxin and *Staphylococcus aureus* (Ricote et al., 1998; Guyton et al., 2003). We have recently reported that 15*d*-prostaglandin J_2 reduces the tissue injury in rodent models of acute and chronic inflammation (carrageenan-induced pleurisy and collagen-induced arthritis, respectively). In that study, 15*d*-prostaglandin J_2 exerted potent anti-inflammatory effects (e.g., inhibition of pleural exudate formation, mononuclear cell infiltration, delayed development of clinical indicators, and histological injury) and reduced the increase in the staining (immunohistochemistry) for nitrotyrosine and poly (ADP-ribose) polymerase and the expression of inducible nitric-oxide synthase and cyclooxygenase-2 in the lungs of carrageenan-treated mice and in the joints from collagen-treated mice (Cuzzocrea et al., 2002). The reduction in myocardial infarct size afforded by 15*d*-prostaglandin J_2 was also associated with the reduced expression of pro-inflammatory proteins including inducible nitric oxide synthase and monocyte chemoattractant protein-1 (Ti-Yue et al., 2001; Wayman et al., 2002).

Thus, the potent PPAR-γ agonist 15*d*-prostaglandin J_2 reduces the liver injury caused by severe endotoxaemia in the rat. The mechanism of the protective effect of the cyclopentenone prostaglandin may involve the inhibition of the transcription factor NF-κB in a PPAR-γ dependent or independent fashion. We propose that 15*d*-prostaglandin J_2 (or other cyclopentenone prostaglandins) or other potent ligands for PPAR-γ may be useful in the therapy of the organ injury associated with endotoxic shock.

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