Lipopolysaccharide-induced myocardial protection against ischaemia/reperfusion injury is mediated through a PI3K/Akt-dependent mechanism

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Aims The ability of lipopolysaccharide (LPS) pre-treatment to induce cardioprotection following ischaemia/reperfusion (I/R) has been well documented; however, the mechanisms have not been fully elucidated. LPS is a Toll-like receptor 4 (TLR4) ligand. Recent evidence indicates that there is cross-talk between the TLR and phosphoinositide 3-kinase/Akt (PI3K/Akt) signalling pathways. We hypothesized that activation of PI3K/Akt signalling plays a critical role in LPS-induced cardioprotection.

Methods and results To evaluate this hypothesis, we pre-treated mice with LPS 24 h before the hearts were subjected to ischaemia (45 min) and reperfusion (4 h). We examined activation of the PI3K/Akt/GSK-3β signalling pathway. The effect of PI3K/Akt inhibition on LPS-induced cardioprotection was also evaluated. LPS pre-treatment significantly reduced infarct size (71.25%) compared with the untreated group (9.3 ± 1.58 vs. 32.3 ± 2.92%, P < 0.01). Cardiac myocyte apoptosis and caspase-3 activity in LPS-pre-treated mice were significantly reduced following I/R. LPS pre-treatment significantly increased the levels of phospho-Akt, phospho-GSK-3β, and heat shock protein 27 in the myocardium. Pharmacological inhibition of PI3K by LY294002 or genetic modulation employing kinase-defective Akt transgenic mice abolished the cardioprotection induced by LPS.

Conclusion These results indicate that LPS-induced cardioprotection in I/R injury is mediated through a PI3K/Akt-dependent mechanism.

KEYWORDS
Lipopolysaccharide; Myocardium; Cardioprotection; TLR/NFκB pathway; PI3K/Akt activity

1. Introduction
Numerous studies have shown that Gram-negative bacterial lipopolysaccharide (LPS) induces myocardial protection.1,2 Specifically, pre-treatment of rats with LPS for 24 h increases myocardial functional recovery in isolated ischaemia/reperfusion (I/R) hearts.3 This effect is not unique to LPS, since lipoteichoic acid (LTA), a cell wall component of Gram-positive bacteria, also reduces infarct size when administered to rats 8–24 h before ischaemia.3 The mechanisms by which LPS or LTA induce cardioprotection have not been fully elucidated.

Recent evidence has demonstrated that innate immune responses, mediated by Toll-like receptors (TLRs), participate in myocardial I/R injury and congestive heart failure.4,5 TLR4-mediated NFκB activation plays an important role in myocardial I/R injury.6–10 We and others have reported that TLR4-deficiency10,11 or modulation of TLR4-mediated NFκB activation4 significantly reduces myocardial injury following I/R, improves cardiac functional recovery, and downregulates inflammatory cytokine and adhesion molecule gene expression.9 Interestingly, TLR4 recognizes both LPS and LTA,12 suggesting that TLR4 agonists will induce cardioprotection. However, the TLR4 agonists must be administered at least 8–24 h prior to induction of I/R in order to be effective. This has been referred to as myocardial pre-conditioning or tolerance.

Phosphoinositide 3-kinases (PI3Ks) and their downstream target serine/threonine kinase Akt (also known as protein kinase B) are a conserved family of signal transduction enzymes which are involved in regulating cellular activation, inflammatory responses, and apoptosis.13 Recent evidence

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has identified cross-talk between TLR signalling and the PI3K/Akt pathway. We and others have reported that the PI3K/Akt signalling pathway may be an endogenous negative feedback regulator and/or compensatory mechanism that serves to limit pro-inflammatory and apoptotic events in response to injurious stimuli. Activation of PI3K/Akt-dependent signalling has been shown to prevent cardiac myocyte apoptosis and protect the myocardium from I/R injury. We have also shown that activation of the PI3K/Akt signalling pathway is associated with decreased myocardial ischaemic injury through modulation of TLR4-mediated signalling. However, it is unclear whether activation of the PI3K/Akt signalling pathway could be a mechanism of LPS-induced cardioprotection.

In the present study, we examined the role of PI3K/Akt signalling in LPS pre-treatment-induced cardioprotection. We observed that pre-treatment of mice with low-dose LPS resulted in significantly increased levels of phospho-Akt and phospho-GSK-3β in the myocardium which positively correlated with cardioprotection. Of greater significance, LPS-induced cardioprotection was abolished in the mice treated with a pharmacological inhibitor of PI3K, as well as in transgenic mice with cardiac specific expression of kinase-defective Akt (kdAkt). Our results indicate that LPS-induced cardioprotection is mediated through a PI3K/Akt-dependent mechanism.

2. Materials and methods

2.1 Experimental animals

Transgenic mice with cardiac-specific expression of kdAkt have been described previously. Wild-type mice (FVB) were bred and maintained in the Division of Laboratory Animal Resources (DLAR) at East Tennessee State University (ETSU). All experiments were done in accordance with the guidelines for the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals published by NIH (NIH Publication No. 85-23, revised 1996). All aspects of the animal care and experimental protocols were approved by the ETSU Committee on Animal Care.

2.2 Experimental model of myocardial ischaemia/reperfusion injury

Myocardial I/R injury was induced as described previously. Briefly, 3-month-old male mice were anaesthetized by isoflurane inhalation before the left anterior descending coronary artery was ligated with 7-0 silk ligature that was tied using a ‘shoestring knot’ over a 1 mm polyethylene tube (PE-10). The chest was compressed briefly to expel intrapleural air and closed leaving one end of the coronary suture protruding from the chest. After completion of 45 min of occlusion, the coronary artery was reperfused by pulling on the exteriorized suture to release the knot. After 4 h of reperfusion, the mice were sacrificed and the hearts were harvested.

2.3 Experimental protocols

To investigate the effects of LPS on the infarct size/area at risk, wild-type mice (n = 8 each group) were pre-treated with or without LPS (0.20 mg/kg) by intraperitoneal (i.p.) injection 24 h before the hearts were subjected to I/R. To examine the role of PI3K/Akt signalling in LPS-induced cardioprotection, wild-type mice (n = 5) were pre-treated 24 h with LPS. An additional group of wild-type mice (n = 5) were injected with the PI3K inhibitor LY294002 (1 mg/25 g body weight, Sigma-Aldrich, St Louis, MO, USA) 1 h before the hearts were subjected to I/R. To examine the effect of LPS pre-treatment on the PI3K/Akt signalling pathway activation, mice were pre-treated with LPS (0.20 mg/kg) by i.p. injection 24 h prior to myocardial I/R. A group of mice (n = 5) were injected with the PI3K inhibitor LY294002 (1 mg/25 g body weight) 15 min before the hearts were subjected to I/R. Sham surgical-operated mice treated with or without LY294002 served as sham controls. The solvent for LY294002 was 0.2% sodium carboxymethylcellulose, 0.25% polysorbate-80 in water. The vehicle was the solvent for LY294002, and each mouse was given 200 μL of solvent by i.p. injection before myocardial I/R. The hearts were harvested at the end of the reperfusion period and the blood was washed out with ice-cold phosphate-buffered saline. A single heart tissue cross-section (2 mm) was taken from each heart at the same anatomical location, immersion-fixed in 4% buffered paraformaldehyde, and embedded in paraffin for the TUNEL assay and caspase-3 activity examination by immunohistochemistry as described previously. The remaining heart tissues were used to isolate cellular proteins as described previously.

2.4 Determination of myocardial infarct size

Infarct size was established by TTC (Sigma-Aldrich) staining as described previously. Briefly, the hearts were removed and perfused with saline on a Langendorff system to wash blood from the coronary vasculature before staining with 1% Evans Blue. Each heart was then sliced horizontally to yield five slices. The slices were incubated in 1% TTC for 15 min at 37°C. The infarct area (white) and the area at risk (red and white) from each section were measured using an image analyser. Ratios of risk area vs. left ventricle (RA/LV) and infarct area vs. risk area (IA/RA) were calculated and expressed as a percentage.

2.5 Western blot

Cytoplasmic proteins were prepared from heart tissues and immunoblots were performed as described previously. Briefly, the cellular proteins were separated by SDS-polyacrylamide gel electrophoresis and transferred onto Hybond ECL membranes (Amer sham Pharmacia, Piscataway, NJ, USA). The ECL membranes were incubated with the appropriate primary antibody (anti-phospho-Akt (Ser473), anti-phospho-GSK3β (Ser9) (Cell Signaling Technology, Inc., Beverly, MA, USA), anti-GSK-3β, anti-Akt, anti-Hsp27 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA), respectively, followed by incubation with peroxidase-conjugated secondary anti-bodies (Cell Signaling Technology, Inc.). The signals were detected with the ECL system (Amer sham Pharmacia). To control for lane loading, the same membranes were probed with anti-GAPDH (glyceraldehyde-3-phosphate dehydrogenase, Biodesign, Saco, ME, USA) after being washed with stripping buffer. The signals were quantified by scanning densitometry using a Bio-Image Analysis System (Bio-Rad). The results from each experimental group were expressed as relative integrated intensity compared with that of control hearts measured with the same batch.

2.6 In situ apoptosis assay

In situ cardiac myocyte apoptosis was examined by the TdT-mediated dUTP nick end labelling (TUNEL) assay (Boehringer Mannheim, Indianapolis, IN, USA) as described previously. Three slides from each block were evaluated for percentage of apoptotic cells using the TUNEL assay. Four slide fields were randomly examined using a defined rectangular field area with the magnification of x200. One hundred cells were counted in each field, and apoptotic cardiac myocytes are presented as the percentage of total cells counted.
2.7 Immunohistochemistry for activated caspase-3

Immunohistochemistry was performed to examine caspase-3 activity in the heart sections using specific anti-capase-3-cleaved antibody (Cell Signaling Technology, Inc.) as previously described. Briefly, hearts from each group were harvested and immersion-fixed in 4% buffered paraformaldehyde, embedded in paraffin, cut at 5 μm, and stained with an antibody directed against activated caspase-3. Three slides from each block were evaluated with bright-field microscopy.

2.8 Statistical analysis

Data are expressed as mean ± SE. Comparisons of data between groups were made using one-way analysis of variance (ANOVA), and Tukey’s procedure for multiple-range tests was performed. P < 0.05 was considered to be significant.

3. Results

3.1 Lipopolysaccharide pre-treatment attenuates myocardial injury following ischaemia/reperfusion

Figure 1 shows that I/R resulted in a significant increase (32.3 ± 2.92%) in infarct size/area at risk (IA/RA), index for myocardial injury). However, infarct size in LPS-pre-treated mice was reduced by 66.5% compared with the I/R group (9.3 ± 1.58 vs. 32.3 ± 2.92, P < 0.01). There is no significant difference in risk area/left ventricle (RA/LV), which reflects the position of coronary artery ligation, between untreated and LPS-pre-treated mice.

3.2 Lipopolysaccharide pre-treatment attenuates cardiac myocyte apoptosis following myocardial ischaemia/reperfusion

As shown in Figure 2A, cardiac myocyte apoptosis was significantly increased in the myocardium of ischaemic hearts compared with sham control (26.4 ± 2.67 vs. 2.7 ± 0.45%). The percentage of cardiac myocyte apoptotic cells in LPS-pre-treated mice was also significantly increased compared with LPS-pre-treated sham control (14.1 ± 0.71 vs. 3.1 ± 1.15) after I/R; however, the increase was significantly less than in the untreated ischaemic hearts (14.1 ± 0.71 vs. 26.4 ± 2.67%). Figure 2B shows that caspase-3 activity was increased in the myocardium following I/R as evidenced by immunohistochemistry with specific anti-capase-3-cleaved antibody when compared with sham control. We observed reduced caspase-3 activity in the myocardium of LPS-pre-treated mice compared with the untreated mice.

3.3 Lipopolysaccharide pre-treatment increases the levels of phospho-Akt and phospho-GSK3β in the myocardium following ischaemia/reperfusion

To investigate whether LPS pre-treatment will induce the activation of PI3K/Akt signalling in the myocardium following I/R, we examined the levels of phospho-Akt in the myocardium. As shown in Figure 3A, LPS pre-treatment significantly increased the levels of phospho-Akt in the myocardium in sham mice (1.25 ± 0.18) compared with untreated sham mice (0.14 ± 0.02). Importantly, the levels of phospho-Akt in LPS-pre-treated I/R hearts were significantly higher than untreated I/R hearts (1.19 ± 0.03 vs. 0.52 ± 0.18). Akt is an important kinase downstream from PI3K. We examined the effect of blocking PI3K activity by LY294002 on LPS-increased levels of Akt phosphorylation in the myocardium. As shown in Figure 3A, administration of LY294002 to mice did not affect the levels of phospho-Akt in the myocardium that was subjected to I/R in the absence of LPS pre-treatment. However, blocking the PI3K activity by LY294002 significantly attenuated LPS-increased levels of Akt phosphorylation both in sham (0.28 ± 0.13) and in I/R (0.41 ± 0.07) hearts. The solvent had no effect on myocardial heart size as published previously.

GSK3β is an important kinase downstream from Akt. As shown in Figure 3B, the levels of phospho-GSK-3β (Ser-9) in the myocardium were significantly higher in the LPS-pre-treated group than in the untreated mice both in sham (0.77 ± 0.06 vs. 0.17 ± 0.03) and in I/R (0.75 ± 0.03 vs. 0.42 ± 0.09). LY294002 administration significantly attenuated LPS-increased levels of phospho-GSK-3β in the myocardium both in sham (0.33 ± 0.05) and in I/R (0.32 ± 0.02) mice.

3.4 Lipopolysaccharide pre-treatment increases Hsp27 levels in the myocardium following ischaemia/reperfusion

Recent evidence has also shown that Hsp27 protects the myocardium from I/R injury and inhibits doxorubicin-induced cardiac myocyte apoptosis. We examined the effect of LPS pre-treatment on the expression of
Hsp27 in the myocardium following I/R. As shown in Figure 4, LPS pre-treatment increased the expression of Hsp27 in the myocardium in sham (1.59 ± 0.23) and I/R (1.79 ± 0.14) groups compared with non-LPS-treated sham (0.90 ± 0.11) and I/R (1.04 ± 0.08) mice. Interestingly, administration of a PI3K inhibitor, LY294002, significantly attenuated LPS-increased levels of Hsp27 both in sham (1.16 ± 0.06) and in I/R (1.19 ± 0.09) mice.

3.5 Pharmacological inhibition of phosphoinositide 3-kinase abrogates the myocardial protection associated with ischaemia/reperfusion injury in lipopolysaccharide-pre-treated mice

To examine whether increased activation of the PI3K/Akt pathway may be responsible for the protection of the myocardi um from I/R injury in LPS-pre-treated mice, we administered the PI3K inhibitor, LY294002, to LPS-pre-treated mice. As shown in Figure 5A, pharmacological inhibition of PI3K with LY294002 abrogated the cardioprotection observed in LPS-pre-treated mice following I/R injury (Figure 5A). The infarct size/area at risk (IA/RA) was significantly greater in LPS+LY294002 (31.1 ± 3.57%, P < 0.05) compared with LPS-pre-treated mice that did not receive the inhibitor (11.9 ± 1.37%). Hearts from mice treated with LY294002 show large infarct areas (white, no TTC staining) when compared with heart sections from LPS-pre-treated mice that were not treated with the PI3K inhibitor. Administration of LY294002 did not significantly affect I/R-induced myocardial infarct size in non-LPS-treated mice.

3.6 Genetic deficiency of Akt abrogates the myocardial protection associated with ischaemia/reperfusion injury in lipopolysaccharide-pre-treated mice

Akt is an important downstream kinase that is phosphorylated and activated by PI3K. We examined the effect of LPS pre-treatment in mice that express a kinase-deficient (inactive) form of Akt (kdAkt). LPS was administered to kdAkt transgenic mice and age-matched wild-type mice served as control. Figure 5B shows that LPS pre-treatment induces cardioprotection in wild-type mice as expected. However, cardioprotection is abolished in kdAkt mice. The infarct size/area at risk in I/R kdAkt mice was not significantly different from that of wild-type mice (Figure 5B). In addition, there is no significant difference in infarct size/area at risk between I/R kdAkt mice and age-matched I/R wild-type mice.

Figure 2 Lipopolysaccharide pre-treatment attenuates cardiac myocyte apoptosis following myocardial ischaemia/reperfusion. Mice were pre-treated with or without lipopolysaccharide 24 h before the hearts were subjected to ischaemia (45 min)/reperfusion (4 h). Sham surgery-operated mice served as sham controls. The hearts were harvested and sectioned for analysis of apoptosis by the TUNEL assay (A) and caspase-3 activity by immunohistochemistry with specific anti-capase-3-cleaved antibody (B). Photographs of representative TUNEL-stained myocardial sections are shown at the right (A). Blue colour indicates the nucleus of each cell, and the dark brown colour indicates positive cardiac myocyte apoptosis which is marked by red arrows. The bar graph shows the percentage of apoptotic cells. *P < 0.01 compared with indicated groups. Caspase-3 activity in the cardiac myocytes is indicated by brown colour staining (B). S, sham; I/R, ischaemia/reperfusion.
4. Discussion

The major finding in this study is that LPS-induced cardioprotection is mediated via a PI3K/Akt-dependent mechanism. We demonstrated that administration of a pharmacological inhibitor of PI3K abrogated the protective effect of LPS pre-treatment in myocardial I/R injury. We also showed that the cardioprotective effect of LPS pre-treatment was abolished in the mice with constitutive expression of a kinase-defective form of Akt (kdAkt). Thus, PI3K/Akt is involved in LPS pre-treatment-induced cardioprotection. To the best of our knowledge, this is the first report which causally links LPS-induced cardioprotection and the PI3K/Akt signalling pathway.

In our initial studies, we observed that pre-treatment of mice with low-dose LPS significantly reduced myocardial infarction following I/R. This observation is consistent with previous reports. LPS is a cell wall constituent of Gram-negative bacteria and a TLR4 ligand that mediates signalling leading to NF-κB activation. We have previously reported that modulation of TLR4-mediated NF-κB activation protects the myocardium from I/R injury. Although administration of a large dose of LPS rapidly induces NF-κB activation and leads to cardiac dysfunction in experimental animals, previous studies have shown that pre-treatment of animals with a small dose of LPS for 24 h results in significant inhibition of NF-κB activation and protection of the myocardium against I/R injury. However, the mechanisms by which LPS inhibited NF-κB activation and protected the myocardium following I/R have not been fully elucidated. In the present study, we observed that LPS pre-treatment increased IkBα levels following I/R (data not shown), suggesting that LPS pre-treatment will induce feedback regulation of IkBα expression in the myocardium.

It is well known that LPS administration will increase the expression of inflammatory cytokines such as TNFα, IL-1β, and IL-6 in the host through the TLR4-mediated NF-κB activation pathway. These inflammatory cytokines play a role in cardiac dysfunction and injury. Recent evidence suggests that the PI3 k/Akt signalling pathway may be an endogenous negative feedback regulator of TLR/NF-κB-mediated...
We and others have previously shown that PI3K/Akt may be a negative feedback mechanism that prevents excessive innate immune and/or inflammatory responses. We observed in the present study that a small dose of LPS pre-treatment significantly increased the levels of myocardial phospho-Akt. We have previously reported that activation of the PI3K/Akt signalling pathway rapidly induces cardioprotection in a rodent model of myocardial I/R injury. Although activation of the PI3K/Akt signalling pathway will negatively regulate TLR/NF-κB-mediated inflammatory responses, recent studies have suggested that there is cross-talk between the TLR and PI3K/Akt signalling pathways. For example, stimulation of TLR2 or TLR4 can result in activation of PI3K/Akt-dependent signalling. Activation of PI3K/Akt-dependent signalling protects cardiac myocytes from I/R injury and inhibits I/R-induced cardiac myocyte apoptosis. We observed that the levels of phosphorylated Akt in the myocardium of LPS-pre-treated mice were higher than those observed in control mice. This is also true for LPS-pre-treated mice that were subjected to myocardial I/R. We speculated that high levels of myocardial PI3K/Akt activity in LPS-pre-treated mice may be responsible for the cardioprotection against I/R injury. To test this hypothesis, we first administered the PI3K inhibitor, LY294002, to LPS-pre-treated mice prior to myocardial I/R. We observed an increased level of phosphorylated GSK-3β in the myocardium of LPS-pre-treated mice which correlated with reduced cardiac infarct size. We conclude that elevated myocardial PI3K/Akt levels in LPS-treated mice result in increased phosphorylation of GSK-3β which may play a role in LPS-induced cardioprotection.

The contribution of cardiac myocyte apoptosis to myocardial injury has been well documented. Pharmacological inhibition of PI3K with LY294002 abrogated cardioprotection in LPS-pre-treated mice following I/R injury. Akt is an important kinase downstream from PI3K. Phosphorylation of GSK-3β by Akt results in inactivation of the enzyme. GSK-3β inhibition protects against organ injury and dysfunction in haemorrhagic shock and endotoxemia. We have previously reported that activation of PI3K/Akt signalling increased the levels of phosphorylated GSK-3β. We speculated that increased myocardial PI3K/Akt activity in LPS-pre-conditioned mice might result in increased phosphorylation of GSK-3β. We observed an increased level of phosphorylated GSK-3β in the myocardium of LPS-pre-treated mice which correlated with reduced cardiac infarct size. We conclude that elevated myocardial PI3K/Akt levels in LPS-treated mice result in increased phosphorylation of GSK-3β which may play a role in LPS-induced cardioprotection.

**Figure 5** Pharmacological inhibition of phosphoinositide 3-kinase (A) and kinase-deficient Akt (B) abrogates the cardioprotection induced by lipopolysaccharide pre-treatment. (A) Mice were pre-treated with and without lipopolysaccharide (n = 8 each group) 24 h before the hearts were subjected to myocardial ischaemia (45 min) followed by reperfusion for 4 h. In the pharmacological inhibition group, mice (n = 8) were pre-treated with lipopolysaccharide for 24 h and were injected intraperitoneally with LY294002 (1 mg/25 g body weight) 1 h prior to ischaemia (45 min) followed by reperfusion for 4 h. (B) Kinase-deficient Akt transgenic mice (kdAkt, n = 8) were pre-treated with or without lipopolysaccharide 24 h before the hearts were subjected to ischaemia (45 min) followed by reperfusion (4 h). The hearts were harvested and infarct size was determined by triphenyltetrazolium chloride staining. Ratios of risk area vs. left ventricle area (RA/LV) and infarct area vs. risk area (IA/RA) were calculated and are presented in the graph. *P < 0.01 compared with the ischaemia/reperfusion group. RA, risk area; LV, left ventricle; IA, ischaemic area; LY, LY294002.
study, we observed that pre-treatment of mice with low-dose LPS significantly attenuated cardiac myocyte apoptosis and caspase-3 activity in isolated rat hearts. Anti-apoptotic effects of activated PI3K/Akt signalling have been well documented. To investigate whether other anti-apoptotic effectors are involved in LPS pre-treatment attenuation of cardiac myocyte apoptosis, we examined the expression of Hsp27 in the myocardium. Recent studies have shown that Hsp27 transgenic mice are protected against myocardial injury caused by I/R or doxorubicin. In the present study, we observed that LPS pre-treatment increased the levels of Hsp27 in the myocardium which was attenuated by PI3K inhibition with LY294002. This observation indicates that there is a link between PI3K/Akt and Hsp27. Thus, we conclude that LPS pre-treatment attenuates cardiac myocyte apoptosis and necrosis by activation of the PI3K/Akt signalling pathway and increased levels of the anti-apoptotic effector Hsp27.

In summary, our data indicate that LPS-induced cardiotoprotection is mediated, in part, through the PI3K/Akt signalling pathway. These data are significant because they demonstrate that activation of the PI3K/Akt signalling pathway plays an important role in protecting the myocardium from I/R injury in LPS-induced cross-tolerance or LPS-pre-conditioning. These data may also point to a possible strategy for reducing heart injury. For example, modulation of TLR4/NF-κB-dependent signalling, while simultaneously stimulating PI3K/Akt-dependent signalling, may decrease the morbidity and mortality associated with myocardial infarction. In addition, the cardioprotective effect was still observed after 24 h administration of LPS which would be of great benefit for many patients, especially those undergoing cardiac bypass surgery or other procedures in which cardiac arrest is needed.

Conflict of interest: none declared.

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