Prenatal lipopolysaccharide exposure causes mesenteric vascular dysfunction through the nitric oxide and cyclic guanosine monophosphate pathway in offspring

Xinquan Wang a,b,1, Jiali Wang a,b,1, Hao Luo a,b, Caiyu Chen a,b, Fang Pei a,b, Yue Cai a,b, Xiaoli Yang a,b, Na Wang a,b, Jinjuan Fu a,b, Zaichen Xu a,b, Lin Zhou a,b,* Chunyu Zeng a,b,*

* Department of Cardiology, Daping Hospital, The Third Military Medical University, People’s Republic of China
b Chongqing Institute of Cardiology, Chongqing, People’s Republic of China

A R T I C L E   I N F O
Article history:
Received 30 January 2015
Received in revised form 3 May 2015
Accepted 26 May 2015
Available online 12 June 2015

Keywords:
Fetal programming
Hypertension
Lipopolysaccharide
Mesenteric artery
Endothelium
Nitric oxide
cGMP
Oxidative stress

A B S T R A C T
Cardiovascular diseases, such as hypertension, could be programmed in fetal life. Prenatal lipopolysaccharide (LPS) exposure in utero results in increased blood pressure in offspring, but the vascular mechanisms involved are unclear. Pregnant Sprague–Dawley rats were intraperitoneally injected with LPS (0.79 mg/kg) or saline (0.5 ml) on gestation days 8, 10, and 12. The offspring of LPS-treated dams had higher blood pressure and decreased acetylcholine (ACh)-induced relaxation and increased phenylephrine (PE)-induced contraction in endothelium-intact mesenteric arteries. Endothelium removal significantly enhanced the PE-induced contraction in offspring of control but not LPS-treated dams. The arteries pretreated with L-NAME to inhibit nitric oxide synthase (eNOS) in the endothelium or ODQ to inhibit cGMP production in the vascular smooth muscle had attenuated ACh-induced relaxation but augmented PE-induced contraction to a larger extent in arteries from offspring of control than those from LPS-treated dams. In addition, the endothelium-independent relaxation caused by sodium nitroprusside was also decreased in arteries from offspring of LPS-treated dams. The functional results were accompanied by a reduction in the expressions of eNOS and soluble guanylate cyclase (sGC) and production of NO and cGMP in arteries from offspring of LPS-treated dams. Furthermore, LPS-treated dam’s offspring arteries had increased oxidative stress and decreased antioxidant capacity. Three-week treatment with TEMPOL, a reactive oxygen species (ROS) scavenger, normalized the alterations in the levels of ROS, eNOS, and sGC, as well as in the production of NO and cGMP and vascular function in the arteries of the offspring of LPS-treated dams. In conclusion, prenatal LPS exposure programs vascular dysfunction of mesenteric arteries through increased oxidative stress and impaired NO–cGMP signaling pathway.

© 2015 Elsevier Inc. All rights reserved.

Introduction
Epidemiological studies show a significant involvement of environmental factors during development in contributing to overall cardiovascular risks at later stages of life in human population [1–3]. This differs from the traditional belief that disease in humans, hypertension, for example, is the result of a complex interaction between genetic susceptibility and environment.

Maternal infection and inflammation, including chorioamnionitis, and periodontal, urinary tract, and respiratory infections [4], are the most common and clinically relevant perturbations during pregnancy, causing a stressful intrauterine environment [5]. During pregnancy, maternal inflammation increases the exposure of the fetus to elevated circulating levels of cytokines, chemokines, and/or lipid mediators [6,7], which could have a harmful effect on fetal development [8]. Periperal administration of LPS derived from Escherichia coli is a well-characterized model of sepsis in rodents [9]. Our previous study showed that prenatal LPS exposure results in increased blood pressure with impairment in sodium excretion, which is ascribed to decreased dopamine-induced natriuresis and diuresis, but with normal plasma creatinine and urea nitrogen levels [10]. In addition, other studies showed that prenatal exposure to LPS leads to impaired aortic reactivity with decreased expression of connexin 37 (Cx37), which plays a role in the regulation of vascular tone and development of the...
vascularity [11–13], via nuclear factor-kB (NF-κB) activation [14], and increased angiotensin type 1/type 2 receptor (AT1/R/AT2/R) ratio [15]. However, the impact on vascular function has not been fully evaluated, especially in smaller mesenteric arteries that contribute considerably to peripheral vascular resistance [16].

The present study examined whether or not prenatal (in utero) exposure to LPS could program dysfunction of mesenteric arteries in the offspring and investigated the possible underlying mechanisms and strategy to restore the impaired vascular function and hypertension in the offspring of LPS-treated dams.

Materials and methods

Animals and treatment

All animal procedures conformed to NIH guidelines for the care and use of laboratory animals, and the experimental protocols were approved by The Third Military Medical University Animal Care and Use Committee in China. Pregnant Sprague–Dawley (SD) rats (260–280 g) were purchased from the Animal Centre of The Third Military Medical University. They were intraperitoneally injected with LPS (0.79 mg/kg, Sigma, St Louis, MO) or saline (0.5 ml) on gestation days 8, 10, and 12 (n = 12 in each group), and housed individually throughout the pregnancy until delivery. All pups were weaned at 4 weeks of age to a regular chow.

Blood pressure was measured biweekly starting at 5 weeks of postnatal age. At 12 weeks of age, the male offspring of control and LPS-treated dams were randomly assigned into two groups: one group drank tap water and served as controls, and the other group drank tap water containing 1 mmol/L TEMPO for 3 weeks. The TEMPO-containing water was changed twice daily. Blood pressure in conscious rats was measured using the tail-cuff method (BP-2010, Softron Beijing Biotechnology Co., China). The food intake was recorded. Fasting plasma glucose was measured with a glucose analyzer (Roche, Indianapolis, IN) at 15 weeks of age.

Reagents and chemicals

Acetylcholine chloride (ACh), phenylephrine (PE), N^6-nitro-L-arginine methylster (L-NAME), 1 H-1,2,4-oxadiazolo-4,3-quinoxalin-1-one (ODQ), and sodium nitroprusside (SNP) were from Sigma-Aldrich (St. Louis, MO). Anti-eNOS antibody (9572) was from Cell Signaling Technology (Boston, MA), anti- nitrotyrosine (sc-55256), Nox2 (sc-5827), Nox4 (sc-21860), SOD1 (sc-11407), SOD2 (sc-18503), AT1R (sc-1173), and GAPDH (sc-25778) antibodies were from Santa Cruz Biotechnology; anti-GC antibody (anti-subunit, 160895) was from Cayman Chemicals (Ann Arbor, MI). Dihydroethidium (DHE), nitric oxide (NO), and cyclic guanosine monophosphate (cGMP) assay kits were from Nanjing Jianchen Bioengineering Institute (Nanjing, China). Angiotensin II (Ang II) assay kit was from Cayman Chemicals (Ann Arbor, MI).

Vascular histology

Histological analysis was performed in mesenteric arteries from the offspring of control and LPS-treated dams at 15 week of age. The first-order branches of the superior mesenteric arteries were quickly removed, carefully dissected, fixed in 4% paraformaldehyde, embedded in paraffin, and then cut into 4-μm-thick sections. The sections were stained with hematoxylin and eosin (H&E).

Preparation of mesenteric arterial rings

At 15 weeks of age, the rats were anesthetized with pentobarbital sodium (50 mg/kg), and the mesenteric bed was removed and immersed in ice-cold physiological salt solution (PSS), containing (in mM) 119 NaCl, 4.7 KCl, 2.5 CaCl_2·H_2O, 1.17 MgSO_4·H_2O, 25 NaH_2CO_3, 1.18 KH_2PO_4, 0.027 EDTA, and 5.5 glucose, adjusted to pH 7.35–7.45. The mesenteric artery was carefully dissected free of the surrounding connective tissues. Third-order branches of the superior mesenteric artery (diameter of 250 ± 20 μm) were cut into 2-mm-long ring segments, and these rings were mounted on a myograph (DMT, Aarhus, Denmark) for isometric tension recording, using Labchart software (AD Instruments, Colorado Springs, CO) [17]. In some rings, the endothelium was removed by gently rubbing the vessel interior with tungsten wire. Removal of the endothelium was verified by the absence of ACh-induced relaxation. Rings were equilibrated for 1 h before the start of the experiment.

Assessment of vascular reactivity

The concentration–contraction curves were studied for PE-induced contraction in endothelium-intact rat mesenteric arteries. In some endothelium-intact rings precontracted by PE at a concentration that produced 80% of the contraction induced in Krebs physiological salt solution (KPSS), ACh was added cumulatively (10^−9–10^−5 mol/L) to induce concentration-dependent relaxation. Endothelium-independent relaxation was also studied in response to sodium nitroprusside (10^−9–10^−5 mol/L). In other experiments, the tissues were pretreated for 30 min with L-NAME (10^−4 mol/L) to inhibit eNOS in the endothelium or with ODQ (10^−5 mol/L) to inhibit cGMP production in the smooth muscle before measuring the effects on PE-induced contraction and ACh-induced relaxation.

Immunoblotting

Mesenteric arterial rings, homogenized in lysis buffer, were ultrasonicated for 15 s, and then centrifuged (12,000 rpm) at 4 °C for 30 min. The supernatants were collected and protein concentration was measured by the Bradford assay. Samples with equal amounts of protein were loaded and separated on SDS-PAGE, and then blotted on nitrocellulose membranes. After blocking with 5% nonfat milk in TBS (Tris-buffered saline) with 0.05% Tween 20 for 0.5 h, the membranes were incubated with anti-eNOS (1:800 dilution), SGC (1:800), nitrosynitrate (1:500), Nox2 (1:400), Nox4 (1:400), SOD1 (1:400), SOD2 (1:400), AT1R (1:600), and GAPDH (1:800) antibodies at 4 °C overnight. The membrane-bound antibodies were visualized using horseradish peroxidase-conjugated secondary antibodies (1:12,000) and the Odyssey infrared imaging System (Li-Cor Bioscience, Bad Homburg, Germany).

NO and cGMP levels

Endothelium-intact mesenteric arteries were placed in test tubes containing 2 mL Krebs solution aerated with 95% O_2/5% CO_2 at 37 °C, and the solution was changed every 30 min for 1 h. The arteries were stimulated with ACh (10^−7 and 10^−6 mol/L) for 5 min, rapidly removed, dabbed dry with filter paper, and weighed. The incubation solution was assayed for the stable end product of NO, i.e., nitrate (NO_3^-) and nitrite (NO_2^-). The endothelium-denuded mesenteric arteries were stimulated with SNP (10^−7 and 10^−6 mol/L) for 5 min, and the tissue level of cGMP was measured by enzyme-linked immunosorbent assay.

ROS measurement

The mesenteric arteries were incubated with the oxidative fluorescent dye dihydroethidium (DHE, 10 μmol/L) for 30 min in a light-protected humidified chamber at 37 °C, briefly washed, and then quickly imaged under a fluorescence microscope.
Statistical analysis

Data are means ± SEM. Statistical analysis was performed using a two-way ANOVA followed by the Bonferroni post hoc test. Contraction was calculated as percentage of the PE-induced maximal tension. ACh-induced relaxation was calculated as percentage reduction of the precontraction value. Half-maximal effective concentrations were determined by regression analysis (GraphPad Software, San Diego, CA) and expressed as negative log molar concentration. *P < 0.05 indicates differences between and among groups.

Results

Effects of prenatal LPS exposure on blood pressure and general parameters in the rat offspring

Blood pressure of rat offspring was monitored biweekly between 5 and 19 weeks of age. The systolic blood pressure (SBP, Fig. 1) was higher in offspring of LPS-treated dams than control dams. The 15-week-old offspring of LPS-treated dams also had greater body weight and food intake than offspring of control dams, consistent with previous reports [10,18,19] (Table 1). There were no differences in heart rate and fasting plasma glucose levels between the two groups at 15 weeks of age (Table 1). There were no obvious differences in gross structure and thickness of the media and intima of the mesenteric arteries between the two groups (Fig. 2).

Effect of prenatal LPS exposure on PE-induced contraction in mesenteric arteries of the rat offspring

Endothelial and smooth muscle cells are known to interact to modulate vascular tone. The vascular endothelium minimizes the vasoconstrictor response to PE [20,21], but such effect is diminished in hypertensive states [22–26]. The difference in PE-induced contractions in the presence of l-NAME or ODQ indirectly reflects the contribution of basal endothelium-derived NO [27]. The present study shows that PE produced greater contractions in endothelium-intact mesenteric arteries from the offspring of LPS-treated than nontreated dams (Figs. 3A and 3C). Treatment with l-NAME (10⁻⁴ mol/L) or ODQ (10⁻⁵ mol/L) augmented PE-induced contractions in arteries from offspring of control but not LPS-treated dams (Figs. 3A and 3C). TEMPOL restored the l-NAME (10⁻⁴ mol/L) or ODQ (10⁻⁵ mol/L) augmented PE-induced contraction in arteries from offspring of LPS-treated dams (Fig. 3D). Similarly, removal of the endothelium enhanced the PE-induced contraction in arteries from offspring of control but not LPS-treated dams (Figs. 4A and 4C). TEMPOL restored the augmented PE-induced contraction in endothelium-denuded arteries from offspring of LPS-treated dams (Fig. 4D).

Effect of prenatal LPS exposure on endothelium-dependent relaxation in rat offspring

In PE-contracted endothelium-intact arteries, the ACh-induced concentration-dependent relaxation was attenuated in offspring of LPS-treated dams (Figs. 5A and 5C). Pretreatment with l-NAME (10⁻⁴ mol/L) or ODQ (10⁻⁵ mol/L) inhibited the ACh-induced relaxation and the remaining relaxations were similar in offspring of control and LPS-treated dams (Figs. 5A and 5C). TEMPOL restored the ACh-induced relaxation in the offspring of LPS-treated dams to the same level as the offspring of control dams with or without l-NAME or ODQ treatment (Fig. 5D). Removal of the endothelium completely inhibited the ACh-induced relaxation in arteries of all groups (data not shown).

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>CT</th>
<th>LPS</th>
<th>LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>276 ± 7</td>
<td>270 ± 11</td>
<td>289 ± 8 *</td>
<td>283 ± 10</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>107 ± 5</td>
<td>106 ± 4</td>
<td>123 ± 4 *</td>
<td>110 ± 5#</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>368 ± 13</td>
<td>370 ± 14</td>
<td>372 ± 11</td>
<td>369 ± 15</td>
</tr>
<tr>
<td>Food intake (g/day)</td>
<td>17.4 ± 1.5</td>
<td>17.0 ± 2.1</td>
<td>21.5 ± 2.6 *</td>
<td>19.9 ± 1.3</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.2 ± 0.4</td>
<td>5.1 ± 0.5</td>
<td>5.4 ± 0.3</td>
<td>5.2 ± 0.4</td>
</tr>
</tbody>
</table>

These data were collected from 15-week-old offspring of vehicle (control)- and LPS-treated dams after treatment with vehicle or TEMPOL (1.0 mmol/L in drinking water) for 3 weeks. CT, Control; TEMPOL; LT, LPS + TEMPOL. Data are means ± SEM of 6–8 experiments.

*P < 0.05 versus control.
# P < 0.05 versus LPS.

Effect of prenatal LPS exposure on endothelium-independent relaxations in rat offspring

The decreased endothelium-dependent vasodilation could be the result of a reduced sensitivity of the vascular smooth muscle to NO. To test this possibility, the effect of the NO donor, SNP, was tested. SNP (10⁻⁶–10⁻⁵ mol/L) produced concentration-dependent relaxations in all four groups, but the SNP-induced relaxation was reduced in endothelium-denuded mesenteric arteries from offspring of LPS-treated dams compared with offspring of control dams. The reduced SNP-induced relaxation of the arteries from offspring of LPS-treated dams was normalized by TEMPOL to the same level as in the controls (Fig. 6).

Effect of prenatal LPS exposure on production of NO–cGMP in offspring rats

The protein expressions of eNOS and sGC (Figs. 7A and 7B) together with basal and ACh-stimulated (10⁻⁷ and 10⁻⁶ mol/L) NO production (Fig. 7C) were lower in endothelium-intact mesenteric arteries from offspring of LPS-treated rats compared with those from control offspring. In addition, the cGMP generation stimulated by SNP (10⁻⁷ and 10⁻⁶ mol/L) was decreased in endothelium-denuded arteries of offspring of LPS-treated dams (Fig. 7D). TEMPOL restored all of the reduced levels observed in offspring of LPS-treated dams to the same levels as that observed in offspring of control dams.

Effects of prenatal LPS exposure on oxidative stress and vascular programming

In vitro and in vivo studies have shown that LPS increases inflammation and ROS production [28,29]. The present study shows...
that the intensity of DHE fluorescence (Fig. 8A), Ang II level, and protein expression of AT1R and its targets, Nox2, Nox4, and nitrotyrosine were all increased in the mesenteric arteries of offspring of LPS-treated dams (Figs. 8B–8F). Conversely, the antioxidant enzymes SOD1 and SOD2 were decreased in mesenteric arteries from offspring of LPS-treated dams compared with offspring of control dams (Figs. 8G and 8H).

We next studied possible mechanisms for beneficial effect of TEMPOL on the mesenteric arterial function. TEMPOL treatment markedly suppressed DHE fluorescence intensity, decreased the levels of Ang II, protein expressions of AT1R, Nox2, Nox4, and nitrotyrosine, and normalized the decreased expressions of SOD1 and SOD2 in mesenteric arteries from offspring of LPS-treated dams without affecting the values from offspring of control dams (Fig. 8).

**Discussion**

Many animal and epidemiological studies suggest that besides genetic and environmental factors, maternal stress can exert
long-lasting influence on physical development, neurochemistry, behavior, and immunocompetence of the offspring [30]. The present study shows that maternal LPS exposure to mimic maternal infection during gestation results in fetal-programmed vascular dysfunction and hypertension in offspring through inhibition of NO–cGMP pathway probably via an increased ROS-dependent mechanism (Fig. 9).

Evidence suggests that an adverse intrauterine environment during a critical period of fetal development causes long-term structural and functional effects in the developing fetus, predisposing it to an increased risk for development of hypertension later in life [31]. LPS from Gram-negative bacteria acts as an endotoxin and a nonspecific immunostimulant [5]. Humans are constantly exposed to low levels of LPS from infection [32]. The model of maternal exposure to LPS is employed to mimic bacterial infection [33], which represents one form of stressful event in the fetus [5]. In our study, the days of gestation for LPS administration were chosen to correspond to the first and second trimesters of human pregnancy, which are the main vulnerable periods of the immune system in response to environmental insults [34]. The dose of LPS (0.79 mg/kg) used was previously reported to induce systemic inflammation with a low incidence of fetal anomalies and no or low rate of abortions [35]. Previous studies have shown the effect of LPS on vascular function in LPS-treated dams, but not in their offspring, and the main effects of LPS are hypotension and depressed arterial contractility [36,37]. However, whether or not exposure of dams to LPS leads to arterial dysfunction in the offspring is not completely known. Other studies and ours suggest that maternal LPS exposure results in increased blood pressure and aortic dysfunction in offspring [10,18,19]; however, those studies used conductance, not resistance, in arteries.

In the hypertensive state, endothelial dysfunction is one of the most common pathological alterations, characterized by enhanced vasoconstriction or/and impaired endothelium-dependent vasodilatation [38]. The present study shows increased PE-induced contraction and decreased ACh-induced relaxation in endothelium-intact arteries from offspring of LPS-treated dams, probably caused by a loss of endothelium-derived NO in those arteries. This notion is supported by the following observations. First, unlike the arteries from control rats, the enhanced PE-induced contraction in arteries from offspring of LPS-treated dams was unaffected by L-NAME or ODQ or by the absence of functional endothelium. Second, the basal and ACh-stimulated NO production, as well as the expression of eNOS, was significantly less in arteries from offspring of LPS-treated dams than those from offspring of control dams. In addition, the endothelium-independent relaxations were also reduced in these arteries without endothelium. Abnormal SNP-induced arterial dilation has also been observed in offspring of pregnant dams fed a high-fat [39] or globally restricted [40], protein-deficient [42], or vitamin D diet [41]. The decreased relaxant responses to SNP are likely caused by decreased sGC expression or intracellular cGMP concentration [42–45]. We found that pretreatment with ODQ (10−5 mol/L) to inhibit cGMP production reduced the ACh-induced relaxation and enhanced PE-induced contraction in the mesenteric arteries of offspring from control but not LPS-treated dams, which were
accompanied by a reduction in both sGC protein expression and SNP-stimulated cGMP production in endothelium-denuded arteries. The present results suggest that the impairment in endothelium-dependent relaxation could be attributed to the impairment in the NO–cGMP signaling in arteries from offspring of LPS-treated dams.

Decreased antioxidant capacity and increased ROS production play an important role in the vascular dysfunction observed in hypertension [46–48]. In the vasculature, NADPH oxidases (NOXs) are the main sources of ROS [48,49]. In addition, NADPH oxidase-derived ROS, including those caused by Nox2 and Nox4, are mainly caused by Ang II via activation of AT1R [50–52]. Previous studies showed that the antioxidant TEMPOL alleviates oxidative stress in animal models of hypertension, and restores both endothelium-dependent and -independent vasorelaxations in rats by normalizing eNOS protein expression and improving NO bioavailability [46,47]. We studied the role of ROS in prenatal vascular programming and found that maternal LPS exposure in dams led to increased mesenteric arterial oxidative stress in their offspring, evidenced by elevation in levels of Ang II, protein expressions of AT1R, Nox2, Nox4, and nitrotyrosine, and ROS production, and also by reduction in the protein expressions of the antioxidants SOD1 and SOD2. The increased oxidative stress most likely accounts for the impaired vasorelaxation, augmented vasoconstriction, and elevated blood pressure. Indeed, 3-week treatment with TEMPOL of LPS-treated dams effectively normalized mesenteric arterial function, expression of various pro- and antioxidant proteins, ROS overproduction, and the elevated blood pressure of their offspring.

Although the exact mechanisms that cause the multiple changes in offspring of dams exposed to LPS are not fully known, the increased ROS production may initiate the pathophysiological

**Fig. 5.** Effects of prenatal LPS exposure on ACh-induced relaxation in the absence or presence of L-NAME (10⁻⁴ mol/L) or ODQ (10⁻⁵ mol/L) in mesenteric arteries from 15-week-old offspring after treatment with vehicle or TEMPOL (1.0 mmol/L) for 3 weeks. (A and B) Offspring of control dams treated with vehicle (A) or TEMPOL (B). (C and D) Offspring of LPS-treated dams treated with vehicle (C) or TEMPOL (D). CT, Control + TEMPOL; LT, LPS + TEMPOL. Data are means ± SEM of experiments in 6 arteries from 6 rats. *P < 0.05 versus arteries treated with L-NAME or ODQ.

**Fig. 6.** Effect of prenatal LPS exposure on SNP-induced relaxation in endothelium-denuded mesenteric arteries from 15-week-old offspring after treatment with vehicle or TEMPOL (1.0 mmol/L) for 3 weeks. CT, Control + TEMPOL; LT, LPS + TEMPOL. Data are means ± SEM of experiments in 6 arteries from 6 rats. *P < 0.05 versus other arteries.
Fig. 7. Effects of prenatal LPS exposure on eNOS (A) and sGC (B) protein expressions, basal and ACh-stimulated NO production in endothelium-intact mesenteric arteries (C), SNP-induced cGMP generation in endothelium-denuded arteries (D) from 15-week-old offspring after treatment with vehicle or TEMPOL (1.0 mmol/L) for 3 weeks. CT, Control + TEMPOL; LT, LPS + TEMPOL. Data are means ± SEM of experiments in 6 arteries from 6 rats. *P < 0.05 versus control rats offspring; #P < 0.05 versus LPS-treated rats offspring.

Fig. 8. Effects of prenatal LPS exposure on ROS levels (reflected by changes in DHE fluorescence intensity (A), tissue Ang II levels (B), and protein expressions of AT1R (C), Nox2 (D), Nox4 (E), nitrotyrosine (F), SOD1 (G), and SOD2 (H) in mesenteric arteries from 15-week-old offspring after treatment with vehicle or TEMPOL (1.0 mmol/L) for 3 weeks. C, Control; CT, Control + TEMPOL; LT, LPS + TEMPOL. Data are means ± SEM of experiments in 6 arteries from 6 rats. *P < 0.05 versus offspring of control dams; #P < 0.05 versus offspring of LPS-treated dams.
Disclosure

There are no conflicts of interest.

Acknowledgments

These studies were supported, in part, by grants from National Natural Science Foundation of China (81470936, 31130029), National Basic Research Program of China (2012CB517801), and Program for Changjiang Scholars and Innovative Research Team in University of Ministry of Education of China (IRT1216).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.freeradbiomed.2015.05.040.

Fig. 9. Schematic illustration of the effect of prenatal LPS exposure on vascular function and blood pressure in offspring. Prenatal LPS exposure to mimic maternal infection in utero results in increased ROS production in offspring, and leads to vascular dysfunction through inhibition of NO–cGMP signaling and ultimately to increased blood pressure.

References
