Thromboxane Receptor Mediates Renal Vasoconstriction and Contributes to Acute Renal Failure in Endotoxemic Mice

JEAN-JACQUES BOFFA,* ARMIN JUST,* THOMAS M. COFFMAN,† and WILLIAM J. ARENDSHORST*

*Department of Cell and Molecular Physiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and †Division of Nephrology, Department of Medicine, Duke University, and Durham VA Medical Centers, Durham, North Carolina

Abstract. Sepsis is a major cause of acute renal failure (ARF) and death. Thromboxane A2 (TxA2) may mediate decreases of renal blood flow (RBF) and/or GFR associated with LPS-induced sepsis. This study tested whether TxA2 receptor blockade, with the use of TxA2 receptor knockout (TP-KO) mice or a selective TP receptor antagonist (SQ29,548), would alleviate LPS-induced renal vasoconstriction and ARF. Under basal conditions, anesthetized TP-KO mice displayed a lower mean arterial pressure than wild-type (WT) mice (102 versus 94 mmHg; \( P < 0.05 \)). RBF, renal vascular resistance (RVR), GFR, and urine flow did not differ among groups under basal conditions, suggesting little tonic influence of TxA2 on renal TP receptors in health. In endotoxemic WT mice, 14 h after LPS (Escherichia coli LPS 8.5 mg/kg intraperitoneally), mean arterial pressure was reduced to 85 mmHg (\( P < 0.001 \)), as were RBF (5.0 versus 9.3 ml/min per g kidney wt; \( P < 0.001 \)) and GFR (0.38 versus 1.03 ml/min per g kidney wt; \( P < 0.001 \)). Heart rate and RVR (71 versus 47 mmHg/ml per min; \( P < 0.05 \)) increased. The decreases in RBF and GFR after LPS were attenuated in TP-KO mice versus WT mice (both \( P < 0.05 \)). In both TP-KO and TP antagonist-treated mice, RVR remained stable in response to LPS versus WT mice that did not receive LPS. Delayed TP-antagonist treatment for 2 h before intravenous LPS abolished the early renal vasoconstriction and alleviated the decrease in GFR. These results demonstrate that renal vasoconstriction during endotoxemic shock induced by LPS is mediated by TP receptors as indicated by pharmacologic blockade and genetic disruption of TP receptors.

Severe sepsis is a systemic inflammatory response to infection associated with coagulopathy, multiple-organ failure, and death. Acute renal failure (ARF) is a common complication of sepsis, which worsens its prognosis. The mortality rate of ARF, characterized by renal vasoconstriction and reduced GFR, is 75% in septic patients, as compared with 45% in patients without sepsis (1). ARF independent of sepsis increases morbidity and mortality (2). During sepsis, an enhancement of renal vascular resistance (RVR) is common, largely independent of a change in mean arterial pressure (MAP) (3). In this regard, renal vasoconstriction markedly contrasts with sepsis-induced generalized systemic vasodilation that includes decreases in MAP and of systemic, intestinal, hepatic, splenic, and nonsplanchnic vascular resistances (4). However, both in experimental models of sepsis and in patients, changes in renal blood flow (RBF) vary widely. Micropuncture studies of renal hemodynamics during endotoxin infusion have shown that GFR and glomerular plasma flow are reduced, primarily as a result of increased afferent arteriolar resistance (5). Other studies show that intraluminal application of LPS in a blood-perfused juxtamedullary nephron preparation elicits a sustained vasoconstriction of the arcuate artery, interlobular artery, and afferent arteriole, without affecting efferent arteriolar diameter. Even greater constriction of the preglomerular vasculature is observed in this preparation in endotoxin-pretreated rats (6). Changes in renal hemodynamics play a major role in ARF because histologic findings in patients with sepsis show only relatively minor focal injury with early preservation of morphology of most glomeruli (7). Similar results are reported from experimental studies (8,9).

Both systemic and local renal vasoactive agents may be involved in the pathogenesis of septic ARF. In this regard, plasma renin activity and plasma concentrations of epinephrine and norepinephrine are increased 16 h after LPS injection. Renal denervation protects against endotoxemia-related ARF (3). In addition to the elevated circulatory levels of catecholamines, other vasoconstrictors such as angiotensin II and vasopressin and locally produced thromboxane A2 (TxA2) may play important roles in septic ARF. Synthesis of TxA2, the major vasoconstrictor of the cyclo-oxygenase (COX) pathways, is increased in the renal cortex after LPS administration (10). Plasma TxB2 concentration, the stable metabolite of
TxA₂, is elevated in an ovine model of hyperdynamic sepsis characterized by increased cardiac output (11). Urinary TxB₂ was markedly elevated, ~15 times, in 455 septic patients who were enrolled in the Ibuprofen in Sepsis Study Group (12). In healthy volunteers, LPS causes a dose-dependent increase in the excretion of TxB₂ concomitant with the stimulation of COX expression in monocytes and neutrophils (13). Moreover, it has been demonstrated in cultured leukocytes that COX-2 expression is inducible, mediated through Toll-like receptor 4 (TLR-4) activation by LPS and NF-κB (14). *In situ* hybridization and immunocytochemical studies of COX isoforms after stimulation with systemic LPS show an upregulation of COX-2 mRNA and protein, mostly in the renal cortex and outer medulla, compared with untreated rats (15). TxA₂ synthesis is also stimulated by Ang II and platelet activating factor (PAF), agents that are elevated during sepsis (16). Intra-aortic infusion of U-46619, a TxA₂ agonist, mimics the fall in GFR and RBF and the increase in RVR commonly associated with LPS injection (17). Independent of its vasoactive action, TxA₂ receptor (TP) receptor stimulation induces platelet aggregation and favors thrombosis, events that are commonly associated with organ failure in septic patients. The improvement of survival rate by activated protein C treatment in patients with severe septic shock emphasizes the primary role of coagulation in organ dysfunction (18). Treatment with ONO 3708, a TP receptor antagonist, is reported to attenuate thrombocytopenia and improve the survival rate of rats in endotoxin shock from 38 to 72% at 24 h (19).

The aim of our study was to assess the role of TxA₂ and TP receptor activation during basal resting conditions and in endotoxin-induced renal vasoconstriction and ARF. We used TP knockout (TP-KO) mice and a selective TP receptor antagonist in wild-type (WT) mice to evaluate the immediate (1 h) and the long-term (14 h) constrictor effects of endogenous TxA₂ on the renal vasculature. Our results demonstrate that TP receptors mediate increased RVR and contribute to the reduced GFR. Pharmacologic and genetic negation of TP receptor function partially protects the kidney from ARF associated with LPS-induced sepsis.

**Materials and Methods**

**Animals**

TP-KO mice were generated and maintained on a Balb C background as described previously (20,21). Genotyping was routinely performed by PCR analysis. Mice were housed in the University of North Carolina at Chapel Hill animal facilities. All animal experiments were performed according to Institutional Animal Care and Use Committee guidelines of the University of North Carolina at Chapel Hill.

**Surgical Preparation**

Body weight of male mice averaged 27 ± 1 g (n = 80). Mice were anesthetized with an intraperitoneal injection of pentobarbital (50 mg/kg) and placed on a servocontrolled heating table that maintained body temperature at 37°C. A tracheotomy was performed, and a tracheal catheter (PE-90) was inserted to facilitate breathing. The right femoral vein was cannulated with three pulled PE-10 catheters for continuous infusion of BSA (2.5%; 10 μl/min) and isosmotic saline solution (0.9% NaCl; 0.3 ml/kg per min). This infusion rate was selected to ensure fluid resuscitation needed in septic conditions. Additional doses of pentobarbital were given intravenously as required. The right femoral artery was cannulated with a tapered PE-100 catheter connected to a pressure transducer (Statham P23 DB) for continuous monitoring of MAP. FITC-inulin (0.25%; Sigma, St. Louis, MO) was added to BSA infusion for determination of GFR by clearance methodology (22). A PE-50 catheter was inserted into the bladder to collect urine. After the mouse was placed on its right side, the left kidney was exposed through a subcostal incision. The left renal artery was dissected gently and isolated from the renal vein for the determination of RBF using a noncannulating transducer connected to an ultrasonic flowmeter (Transonic system TS420, Ithaca, NY; 0.5-V probe). After completion of surgery, the animals were allowed to stabilize for at least 45 min before measurements commenced. FITC fluorescence in plasma and urine was measured using a Zeiss fluorescence microscope with a ×10 lens and an Orca-II cooled CCD camera.

**Experimental Protocols**

**Protocol 1.** Either isotonic saline (10 ml/kg) or LPS (*Escherichia coli* serotype 026:B6, 8.5 mg/kg in 10 ml/kg) was injected intraperitoneally 14 h before measurements of renal function. A third group received an intravenous infusion of a selective TP receptor antagonist (SQ29,548, 2 mg/kg bolus, 2 mg/kg per h intravenously) continuously during the surgery and the experiment. Thus, TP receptor antagonist treatment in these animals followed LPS injection by 12 h. Preliminary studies established that the dose of SQ29,548 used completely abolished the 40% increase in MAP and the 26% decrease in RBF produced by TxA₂ agonist (U-46619) infused at 7 μg/kg per min.

**Protocol 2.** For exploring the role of TP receptor function in the early phase of endotoxin-induced ARF, two other groups of WT mice were studied before and 1 h after acute intravenous injection of LPS (5 mg/kg). One group received SQ29,548 treatment (2 mg/kg bolus, 2 mg/kg per h at 0.3 ml/kg per min) during surgery and the observation periods. The control group of WT mice received isotonic saline at the same infusion rate.

Observations (protocol 1 and 2) were made on mice during two 30-min control clearance experimental periods. At the end of each period, 10 μl of blood was collected for FITC and hematocrit determination. At the end of an experiment, the left kidney was weighed.

**Statistical Analyses**

Data are expressed as mean ± SEM. Comparisons among groups were determined by one-way ANOVA followed by unpaired *t* test, using SigmaStat software. A paired *t* test was used to detect differences produced by LPS in the protocol 2. χ² test was used to compare the mortality rate. *P* < 0.05 was considered statistically significant.

**Results**

**Effect of TP Receptor Blockade during Basal Conditions**

Results are summarized in Table 1. Under basal conditions, TP-KO mice displayed a lower MAP than WT mice (94 ± 2 versus 102 ± 2 mmHg; *P* < 0.01). However, acute SQ29,548 treatment did not modify basal MAP in WT mice (105 ± 2 versus 102 ± 2 mmHg; *P* > 0.3). Renal hemodynamics (RBF, RVR, and GFR) as well as urine flow and heart rate (HR) were not different among the three groups of mice under basal conditions.
Effects of LPS Injection on Renal Hemodynamics in WT Mice

In WT mice, 14 h after LPS, MAP was reduced by 17% to 85 ± 3 mmHg (P < 0.001), with a concomitant 18% increase in HR to 651 ± 22 beat/min (P < 0.05; Table 1, Figure 1).

Table 1.

Renal hemodynamics in control mice and in endotoxemic mice given LPS 14 h earlier.

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>TP-KO</th>
<th>WT + TP Antag</th>
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<tr>
<td><strong>Mean arterial pressure (mmHg)</strong></td>
<td>85 ± 3</td>
<td>85 ± 3</td>
<td>85 ± 3</td>
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<tr>
<td><strong>Renal blood flow (ml/min per g kidney wt)</strong></td>
<td>5.0 ± 0.5</td>
<td>5.0 ± 0.5</td>
<td>5.0 ± 0.5</td>
</tr>
<tr>
<td><strong>Renal vascular resistance (mmHg/ml per min)</strong></td>
<td>71 ± 8</td>
<td>71 ± 8</td>
<td>71 ± 8</td>
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<tr>
<td><strong>GFR (ml/min per g kidney wt)</strong></td>
<td>0.38 ± 0.04</td>
<td>0.38 ± 0.04</td>
<td>0.38 ± 0.04</td>
</tr>
<tr>
<td><strong>Urine flow (l/min)</strong></td>
<td>7.3 ± 1.2</td>
<td>7.3 ± 1.2</td>
<td>7.3 ± 1.2</td>
</tr>
<tr>
<td><strong>Heart rate (beat/min)</strong></td>
<td>106.3 ± 22</td>
<td>106.3 ± 22</td>
<td>106.3 ± 22</td>
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<tr>
<td><strong>Kidney weight (g)</strong></td>
<td>0.2 ± 0.03</td>
<td>0.2 ± 0.03</td>
<td>0.2 ± 0.03</td>
</tr>
<tr>
<td><strong>No. of animals</strong></td>
<td>10</td>
<td>10</td>
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* C, control; LPS, 14 h after LPS 8.5 mg/kg intraperitoneally; WT, wild-type mice; TP-KO, Thromboxane receptor knockout mice; WT + TP antagonist, wild-type mice given TP receptor antagonist SQ29,548 (2 mg/kg bolus + 2 mg/kg per h) for 2 h starting 12 h after saline (control) or LPS injection intraperitoneally. Data are means ± SEM.

** P < 0.01, WT versus TP-KO.
*** P < 0.001, WT versus TP-KO.
### P < 0.001, WT-LPS versus TP-KO-LPS and TP antagonist-LPS mice.

Figure 1. Renal hemodynamics 14 h after saline and intraperitoneal LPS injection in control and TXA2 receptor knockout (TP-KO) mice, respectively. Open bars, control (saline injection); hatched bars, LPS injection; white bars, wild-type (WT) mice; light gray, TP-KO mice; dark gray, TP antagonist–treated mice. Values are means ± SEM.

Control versus LPS-injected mice, *P < 0.05, **P < 0.01, ***P < 0.001. WT-LPS versus TO-KO-LPS and TP antagonist-LPS mice, #P < 0.05, ##P < 0.01.
RBF and GFR decreased in septic mice by 46 and 63%, respectively \((P < 0.001)\), as compared with values in saline-injected control mice. In contrast to the vasodilation commonly reported for most nonrenal vascular beds, we observed an increase in RVR in the kidneys of endotoxemic mice in the presence of a lower MAP (Figure 1). Surprisingly, urine flow was unaffected on average by LPS.

The acute response to LPS was evaluated in paired studies of another group of experimental animals. The early responses of MAP and renal hemodynamics, assessed 1 h after LPS injection (5 mg/kg intravenously), were similar to that seen 14 h after LPS administration. LPS induced a 17 ± 2% decrease in MAP, with a 7 ± 2% rise in HR. RBF and GFR decreased by 32 ± 2% and 68 ± 9%, respectively, and RVR increased by 21 ± 4% (Figure 2).

Effects of TP Receptor Blockade on Renal Vasoconstriction and ARF Induced by Endotoxin

Mortality rate at 14 h was similar in LPS-injected WT and TP-KO mice (30 and 37%; \(P > 0.8\)). At 14 h, HR, MAP, and urine flow exhibited similar changes in response to LPS in all three groups (Table 1). The reductions of RBF were attenuated to a greater extent in both TP-KO and TP receptor antagonist–treated mice as compared with WT control mice \((P = 0.01; \text{Figure 1})\). RVR in TP-KO and TP receptor antagonist–treated mice was not increased during endotoxemia, in contrast to that observed in WT mice. Renal vasoconstriction was reduced as RVR was less in mice that received TP receptor antagonist versus WT mice \((71 ± 8 and 42 ± 4 \text{ mmHg/ml per min}; P < 0.02)\). Genetic deletion of TP receptors by gene targeting partially attenuated the reduction in GFR \((0.53 ± 0.04 \text{ versus } 0.38 ± 0.04 \text{ ml/min per g kidney wt}; P < 0.03)\) during septic shock. However, delayed antagonism of TP receptors 12 h after LPS administration failed to restore GFR \((0.48 ± 0.05 \text{ ml/min per g kidney wt}; P > 0.15; \text{Figure 1})\).

TP Receptor Mediated the Early Vasoconstriction during Sepsis

To establish an immediate protective effect of TP receptor blockade on the renal vasoconstriction and reduced GFR associated with sepsis, we pretreated mice with TP receptor antagonist and studied them 1 h after intravenous LPS injection. Absolute changes produced to LPS are summarized in Figure 2. The acute systemic response to LPS was similar in the two groups (Figure 2). MAP fell –21 ± 2% in TP antagonist–treated mice versus –17 ± 2% in control mice, and HR rose 12 ± 5% in TP antagonist–treated mice versus 7 ± 2% in control mice. Previous TP receptor blockade attenuated the short-term sepsis-induced reductions of RBF (–18 ± 4 versus –32 ± 2%; \(P < 0.05\)) and of GFR (–44 ± 7 versus –68 ± 9%; \(P < 0.05\)). SQ29,548 treatment abolished the increase in RVR (–4 ± 8 versus 21 ± 4%; \(P < 0.05\)). Urine flow did not change in either group.

Discussion

The mechanisms responsible for renal vasoconstriction and decrease in GFR during sepsis are unknown. No efficient treatment is available to reverse these deleterious characteristics of ARF; thus, ARF treatment today is more “supportive” than curative (23). Alterations in renal hemodynamics seem to be playing a major causative role because the decrease in GFR occurs without evidence of significant tubular obstruction and
with only modest early kidney injuries, other than ischemia. Our major findings are that the early and sustained phases of renal vasoconstriction in ARF produced by LPS are mediated by TP receptor activation and, to a lesser extent, the reduction in GFR. We demonstrate that TP receptor blockade abolishes the increase in RVR, lessens the reduction in RBF, and attenuates the fall of GFR normally characteristic of sepsis induced by LPS. The same conclusions are reached on the basis of our results obtained with pharmacologic blockade of TP receptors or genetic deletion of TP receptors. However, TP receptors have a minor role on renal hemodynamics during unstressed conditions as evidenced by similar values of RBF and GFR between TP-KO and WT mice under control conditions and by the lack of acute effect of the TP receptor antagonist.

The role of TP receptor on renal hemodynamic changes was studied in a standard experimental model of sepsis (3,9). The relevance of this model was recently highlighted by the discovery of LPS signaling pathways leading to inducible nitric oxide synthase (iNOS) and COX-2 gene stimulation (24,25). TLR-4 is the primary molecule through which LPS activates cells, leading to a rapid release of cytokines such as TNF, IL-1, and PAF. It is noteworthy that the C3H/HeJ strain of mice with a homozygous mutation in the TLR-4 gene does not develop LPS-induced ARF and is resistant to LPS-induced mortality (26). In our experiments, we selected a relatively high dose of LPS (8.5 mg/kg intraperitoneally) to mimic the septic shock in humans and to produce a 30% mortality rate at 14 h. Earlier studies used 5 mg/kg intraperitoneally with a stated “low level” of mortality and no decrease in MAP (3). Likewise, we focused on a relatively late phase of sepsis to simulate a short window of undiagnosed clinical sepsis and to determine whether the efficacy of TP blockade would be preventive and/or curative.

In addition, saline was infused at a relatively high rate to favor a hyperdynamic phase of sepsis and mimic fluid resuscitation recommended during human sepsis (27,28).

Under our experimental conditions, we found a lower MAP (−8 mmHg) measured via an indwelling catheter agreeing well with previous tail-cuff measurements of lower systolic BP in TP-KO mice during conscious conditions (20). As previously found in humans, dogs, and rats, TP receptor antagonist treatment did not affect MAP in normal mice (29–31). We assessed for the first time RBF and GFR in the TP-KO mice and found that these hemodynamic measures did not differ among WT mice, TP-KO mice, and mice that were treated with TP receptor antagonist. Likewise, TP receptor antagonist or TxA2 synthase inhibitor does not affect RBF and GFR or tubuloglomerular feedback control of afferent arteriolar resistance in various strains of rat under resting conditions (17,31,32). These results suggest that TP receptors during basal conditions, in contrast to various renal disorders, do not influence renal hemodynamics.

The combined responses of the systemic nonrenal vasculature to LPS are characterized by decreases in MAP and in total peripheral vascular resistance largely as a result of iNOS stimulation and enhanced NO overproduction (33). In accordance with this, we find a greater MAP response to the unselective NO synthase inhibitor, NG-nitro-L-arginine methyl ester in endotoxemic mice than in control mice (data not shown). In contrast to the BP response, the renal circulation responded differently to LPS than did most vascular beds. It is important to recognize that an increase of RVR contributes to the lower RBF in endotoxemic mice. In normal conditions, autoregulatory mechanisms attempt to maintain RBF constant during hypotension by decreasing RVR. Despite the accompanying hypotension, we found a marked renal vasoconstriction during endotoxemic shock, a finding implicating active involvement of vasoactive factors. Our results showing renal vasoconstriction and increased RVR agree with previous in vitro and in vivo studies in rodents (5,6,10).

The origin of the relatively unique constrictor response of the renal microcirculation to LPS is unknown. There is little doubt that there are heterogeneous responses to vasoactive agents among organs and vascular beds. The renal circulation relative to others is commonly spared from the typical agonist hyporesponsiveness seen in endotoxemic conditions (34,35). Furthermore, in contrast to the impaired contraction of isolated aorta to α-adrenoceptor stimulation, contractions to a TxA2 agonist were unaffected by LPS infusion (34). Thus, it is reasonable to postulate that the absence of hypocontractility to TxA2 seems central to the renal vasoconstriction and emphasizes the primary role of TP receptors on renal hemodynamics during sepsis. These notions raise important questions about heterogeneous TP receptor expression and/or TxA2 synthesis between kidney and other tissues during endotoxemic shock.

Our results convincingly demonstrate that the renal vasoconstriction during endotoxemic shock is due to activation of TP receptors. We found that TP receptors mediate both the early and the sustained increase in RVR and contribute to reductions in RBF and in GFR induced by LPS. Furthermore, despite this major vasoactive effect of TxA2, the decrease in GFR was attenuated in part but not completely prevented in TP-KO mice. Independent of TP receptor activation, the apparent absence of autoregulatory vasodilation in response to the decrease in MAP may contribute to the persistent decreases in RBF and GFR. In this regard, impaired endothelium-dependent dysfunction and impaired renal vasodilation are well documented during endotoxemia in humans and animals (36,37). Of related interest, NO production attenuates the myogenic contribution to RBF autoregulation (A.J. and W.J.A., unpublished observations). TP receptor antagonist treatment started 12 h after LPS, when ARF had already been initiated, did not restore the preexisting reduction in GFR. It is unlikely that a longer treatment of TP receptor antagonist would change the outcome of such an established form of ARF, because the benefit on GFR was relatively modest in TP-KO mice. That only partial protection was afforded is clinically relevant. Other investigators have reported that pretreatment with a TxA2 synthase inhibitor prevented the fall in RBF and partially blunted the reduction of GFR 50 min after LPS administration in rats (10). Similar results were obtained in a model of systemic sepsis with ARF secondary to peritonitis in sheep in which a TxA2 synthase inhibitor had a protective effect on GFR (38).

At least four different mechanisms seem to be involved in the renal vascular response to sepsis: (a) COX-2 expression is
stimulated by LPS in white cells and in the renal cortex and medulla, leading to an increase in TxA2 synthesis, resulting in high plasma and urinary TxB2 concentrations, in both septic patients and experimental models (14,15). (b) The cytokines TNFα, IL-1, IFNγ, and PAF are released systematically and provoke the classical overwhelming inflammatory response to LPS injection. Among them, PAF has a major role in sepsis-induced ARF via its vasoconstrictor and platelet aggregate effects. It is interesting that the renal hemodynamic effects of PAF are largely due to release of TxA2 and TP receptor activation. PAF is known to stimulate the glomerular synthesis of TxA2 in a dose-dependent manner (39). Pretreatment with a selective TP receptor antagonist prevents PAF-induced reduction of renal plasma flow and GFR in the rat (40). Furthermore, TxA2 can modulate TNF-α synthesis. A TxA2 synthase inhibitor is known to suppress TNF-α release from peritoneal macrophages (41). In response to LPS, TNF-α plasma concentration was lower in TP-KO mice and WT mice that were treated with either TP antagonist or TxA2 synthase inhibitor compared with WT (42). (c) In addition, other vasoconstrictors, such as leukotrienes and isoprostanes that are elevated during inflammation and sepsis, may participate in renal vasocostricton through TP receptor activation. Their action versus that of TxA2 on TP receptors could be elucidated using thromboxane synthase inhibitor (43). (d) A recent report suggested that the lack of TP receptor activation increases iNOS expression and NO production stimulated by cytokines in smooth muscle cells from TP-KO mice. Consistent with this notion, a TP receptor agonist was found to inhibit cytokine-induced iNOS-NO, suggesting a negative regulatory role of TxA2 on the iNOS-NO system in the vasculature (44). It is tempting to speculate that a higher TxA2 synthesis predominates in the kidney during sepsis, acting to decrease local NO production and worsen its own effect on the renal vasculature. Although the MAP depressor response to sepsis does not differ among groups, TP receptor antagonist or TP receptor deletion improved RBF and reduced RVR, a finding consistent with this notion.

The role of TP receptor in vasocostricton induced by LPS is not limited exclusively to the kidney. For example, a TP receptor antagonist blocks the pulmonary vasocostricton and bronchoconstriction of the early characteristic phase elicited by endotoxin in swine (45). Likewise, a TP receptor antagonist effectively attenuates the acute Staphylococcus toxin-induced coronary vasocostricton in an isolated-perfused heart (46). Hepatic microcirculary dysfunction including intracellular adhesion molecule-1 expression and leukocytes adhering to vessels during endotoxemia were minimized in TP-KO mice in comparison with that in WT counterparts (42).

The less-than-complete preventive effect of TP receptor blockade on the reduction of GFR implicates the involvement of other mediators in the pathogenesis of sepsis-induced ARF. Cytokines, especially TNF-α and IL-1, have been shown to be critical mediators of septic shock and ARF (47,48). However, anti-TNF and anti-IL-1 therapies result in little benefit for patients with severe sepsis. An important consideration is the timing of the therapeutic intervention. The acute kinetics of most cytokines provides an extremely narrow therapeutic window for effective use of inhibitors. Recently, a high mobility group box-1 protein (HMGB-1) was identified as a late mediator of sepsis; inhibition of HMGB-1 activity increased survival and reduced renal injury in a murine model of sepsis (49). Likewise, delayed ethyl pyruvate treatment, which reduces circulating levels of HMGB-1, confers protection against lethality and ARF induced by endotoxemia or sepsis secondary to cecal puncture (9,50).

In summary, TxA2 during normal resting conditions has a minor role on renal hemodynamics. However, mice that are exposed to LPS develop hypotenion and ARF with an inappropriate renal vasocostricton. We demonstrated that TP receptor blockade, both pharmacologically and genetically, abolishes the renal vasocostricton and alleviates reductions in RBF and in GFR observed in endotoxemic shock. This effect may result from an increase in TxA2 synthesis via COX-2 stimulation and cytokines released secondary to LPS. Despite several pathways involving TP receptors, additional treatment is required to restore more effectively the reduced GFR during endotoxemic shock.

Acknowledgments

This work was supported by the National Institutes of Health Research Grant HL-02334, the Research Service of the department of Veterans Affairs, and the Institut National de la Santé et de la Recherche Médicale.

We are grateful to Richard E. Cheney, Department of Cell and Molecular Physiology, University of North Carolina at Chapel Hill, for technical support.

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