CardioRenal Medicine

Cardiorenal Med 2017;7:276–283
DOI: 10.1159/000475846
Published online: June 24, 2017

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Review

The Role of Endotoxin in the Setting of Cardiorenal Syndrome Type 5

Anna Clementi[a, b] Grazia Maria Virzì[a, c] Alessandra Brocca[a, c, d]
Claudio Ronco[a, c]

[a]IRRIV-International Renal Research Institute Vicenza, Vicenza, [b]Department of Nephrology and Dialysis, San Giovanni Di Dio Hospital, Agrigento, [c]Department of Nephrology, Dialysis and Transplant, San Bortolo Hospital, Vicenza, and [d]Department of Medicine DIMED, University of Padova Medical School, Padova, Italy

Keywords
Endotoxin · Lipopolysaccharide · Cardiorenal syndrome type 5

Abstract
Lipopolysaccharide or endotoxin, the major cell wall component of gram-negative bacteria, plays a pivotal role in the pathogenesis of sepsis. It is able to activate the host defense system through the interaction with Toll-like receptor 4, thus triggering pro-inflammatory mechanisms. When the production of inflammatory mediators becomes uncontrolled and excessive, septic shock develops with multiple organ dysfunction, such as myocardial and renal impairment, which are hallmarks of cardiorenal syndrome type 5. In this review, we will analyze the role of endotoxin in the pathogenesis of sepsis, its effects on cardiac and renal interactions in the setting of cardiorenal syndrome type 5 and the possible use of extracorporeal therapies in this clinical condition.

Lipopolysaccharide and Toll-Like Receptor 4 Complex

Lipopolysaccharide (LPS) or endotoxin, the major constituent of the outer membrane of gram-negative bacteria, has been implicated in the pathogenesis of sepsis since the 1800s, when it was first discovered as a gram-negative cell wall toxin responsible for lethal shock [1, 2]. Endotoxin consists of three distinct regions which differ genetically, structurally, and antigenically: a hydrophobic membrane anchor called lipid A; a short chain of sugar residues with multiple phosphoryl substituents defined the core oligosaccharide; and a serospecific polymer

G.M.V. and A.C. contributed equally to this work.

Dr. Grazia Maria Virzì
Department of Nephrology, Dialysis and Transplantation
International Renal Research Insititute Vicenza (IRRIV), San Bortolo Hospital
Via Rodolfi 37, IT–36100 Vicenza (Italy)
E-Mail graziamaria.virzi@gmail.com

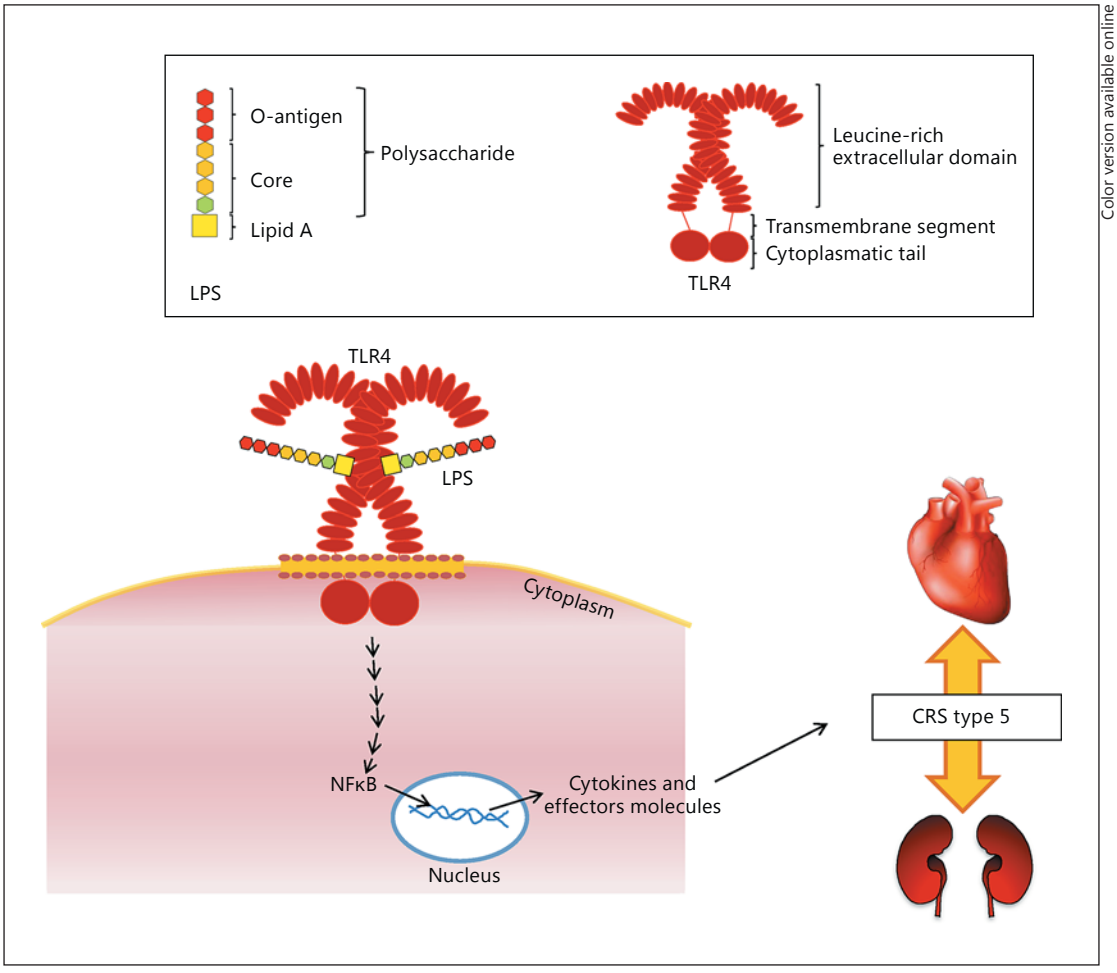

Fig. 1. LPS and TLR4 interactions in CRS type 5.

composed of oligosaccharide repeat units called the O-antigen. The lipid A part is responsible for the endotoxic effect of LPS, and its structure is highly conserved among the different species. Endotoxin binds to the host receptor Toll-like receptor 4 (TLR4) which belongs to the family of Toll receptors, characterized by a large, leucine-rich extracellular domain, a single transmembrane segment, and a short cytoplasmic tail. TLR4 is present on the surface of various cells, including neutrophils, monocytes, and macrophages. In the setting of sepsis, where LPS is abundant, TLR4 inappropriately activates the immune system, thereby triggering an inflammatory response and extensive organ injury [3]. In case of infectious disease, indeed, TLR4 recognizes and binds to LPS, subsequently activating downstream signaling [4] (Fig. 1). The importance of TLR4 as an LPS receptor is highlighted by TLR4-deficient mice being completely resistant to LPS effects. These TLR4-deficient animals do not demonstrate characteristic signs of endotoxic shock after the exposure to LPS [5, 6].

Subsequent events are mediated by TLR4 and an adaptor molecule, MD-2 (myeloid differentiation 2 protein), which is responsible for LPS recognition and the activation of the receptor complex [7–9]. TLR4 is the only TLR that can convey the activating signal through two distinct intracellular pathways involving both myeloid differentiation primary response gene 88 (*MyD88*)-dependent and *MyD88*-independent signaling events [10]. Both pathways result in the translocation of the mammalian transcription factor, nuclear factor κB, with consequent

upregulation of pro-inflammatory cytokines as well as a co-stimulatory molecule for T-cell activation [11]. When the production of inflammatory mediators becomes uncontrolled and excessive, septic shock develops with multiple organ dysfunction, such as myocardial and renal impairment, which are hallmarks of cardiorenal syndrome type 5 (CRS type 5) [12–16] (Fig. 1).

In this review, we will analyze the role of endotoxin in the pathogenesis of sepsis, its effects on cardiac and renal interactions in the setting of CRS type 5, and the possible use of extracorporeal therapies in this clinical condition.

Endotoxin Effects in CRS Type 5

CRS type 5 is characterized by simultaneous cardiac and renal dysfunction in the setting of an extensive spectrum of systemic disorders, such as sepsis, autoimmune disorders, and drug toxicity [17–19]. In CRS type 5 secondary to sepsis, the heart and the kidney are both targets of a strong systemic inflammatory reaction with marked cellular and molecular changes within a time-specific pattern [20].

Cardiac dysfunction during sepsis is characterized by decreased cardiac contractility, impaired ventricular response to fluid therapy, and progressive ventricular dilatation [21, 22]. Tavernier et al. [23] investigated the contractile function of cardiac myocytes isolated 12 h after LPS-induced sepsis (endotoxemia: 5 mg/kg intravenous *Escherichia coli* LPS) in conscious rats. Cardiomyocytes from LPS-injected rats showed depressed twitch shortening compared with cardiomyocytes from control rats. Anyway, the molecular mechanisms involved in the pathogenesis of myocyte impairment induced by LPS remain largely unclear. Two pathogenetic hypotheses have been proposed to explore this mechanism. According to the first one, LPS might induce a direct activation and depression of myocytes, whereas the second one suggests an involvement of immune cells (nonmyocyte sources), such as heart tissue macrophages, mast cells, and infiltrating blood leukocytes (neutrophils and monocytes), responding to LPS and depressing myocyte function [3]. Furthermore, inflammatory cytokine release, mitochondrial dysfunction, cell death and autonomic dysregulation might be involved in the pathophysiology of myocardial dysfunction secondary to sepsis [24]. Indeed, circulating factors, such as TNF-α, IL-1β, lysozyme c, and endothelin-1 have direct inhibitory effects on myocyte contractility, thus participating in the pathogenesis of septic cardiomyopathy [24].

Endotoxin-induced renal dysfunction has been widely described in humans as well as in experimental models of endotoxemia, sepsis, and septic shock [14–16]. Indeed, endotoxin administration is associated with a vast array of local and systemic effects induced by the production of active mediators, responsible for the impairment of renal blood flow, glomerular filtration rate, and tubular dysfunction [25]. Septic acute kidney injury (AKI) is characterized by renal arterial vasodilation and preserved overall renal blood flow [26–28], the so-called hyperemic AKI [29]. Glomerular filtration rate and cellular perfusion have been demonstrated to decrease even if overall renal blood flow is increased due to disproportionate vascular resistance between the afferent and efferent arterioles, regional microvascular flow rates, or renal venous congestion [30, 31], which is often related to the fluid therapy administered during the first hours after ICU admission. Moreover, in a hyperdynamic endotoxemic pig model, despite a significant increase in overall kidney blood flow after LPS administration, almost all of the increased blood flow has been found to be shunted to the medulla, with no increase in cortical blood flow [32]. Therefore, septic AKI might be considered as the consequence of a dysfunction of the renal microvascular system, the direct interaction of pathogen fragments with renal resident cells, the cytotoxic effects of the sepsis-induced cytokine storm, and finally the deleterious crosstalk between damaged organs [33].

Table 1. Summary of studies on CRS type 5

Author, year	Study populations	Plasma mediators	Cytotoxicity in RTC	Apoptotic pathways in RTC
Brocca et al. [44], 2015	11 patients CRS type 5 (ICU)	increased levels of IL-6, -10, -8, -1β, and IFN-γ	induction of cell apoptosis and necrosis	activation of caspase-3, -8 and -9
	16 healthy controls			
Virzi et al. [45], 2016	6 patients CRS type 5, positive EAA	increased levels of IL-6 and IFN-γ	induction of cell apoptosis no differences in cell necrosis and viability	activation of caspase-3 and -8 no differences in caspase-9
	5 patients CRS type 5, negative EAA			

EAA, endotoxin activity assay.

At the molecular level, TLR4 mRNA has been detected in human kidney tissue, as well as in murine renal cortex both in proximal and distant tubules, in the Bowman capsular epithelium, and in the medulla, even if at lower levels [34]. In animal models of systemic gram-negative sepsis, a strong TLR4 signal has been shown in all tubules, both proximal and distal [35, 36], in glomeruli and peritubular capillaries as well, and co-localized with CD14 expression. After the interaction between LPS and TRL4, renal alterations develop in addition to the systemic effects of LPS [35, 36]. Indeed, endotoxin has been reported to decrease the expression of the endocytic receptors megalin and cubilin in the apical compartment of proximal tubular epithelial cells, leading to an interference with the normal processes of protein reabsorption and contributing to the typical low-molecular-weight proteinuria of septic patients [37].

Furthermore, tubular swelling and vacuolization, severe inflammation, oxidative stress, and widespread apoptosis have been described in the setting of gram-negative sepsis [38–40]. In particular, several studies have demonstrated a more prominent role of apoptosis rather than pure necrosis in the pathophysiology of septic AKI [41]. Lerolle et al. [42] analyzed 19 kidney biopsies from patients with septic shock and compared them with biopsies taken from 8 trauma patients and 9 patients with nonseptic AKI. Acute tubular apoptosis was demonstrated by different techniques in patients with septic AKI, whereas almost no apoptosis was detected in patients with nonseptic AKI. Moreover, in an experimental model of cultured human proximal tubular cells, Jo et al. [43] demonstrated that endotoxin, TNF-α and other pro-inflammatory cytokines induced apoptosis of renal proximal tubular cells.

In specific regard to CRS type 5, Brocca et al. [44] reported that plasma from patients with CRS type 5 was able to trigger a response in renal tubular cells (RTCs), resulting in increased apoptosis and loss of cellular viability. The authors analyzed 11 CRS type 5 patients and 16 healthy subjects. RTCs incubated with CRS type 5 plasma showed significantly higher apoptosis and necrosis levels compared with controls, with activation of caspase-3, caspase-8, and caspase-9 [44]. A possible relationship between endotoxin levels and renal cell death in septic patients with CRS type 5 has been suggested by the same authors [45]. RTCs incubated with plasma from endotoxin-positive patients showed significantly higher apoptosis levels and higher caspase-3 activation compared to cells incubated with plasma from endotoxin-negative patients, and a significant positive correlation was observed between endotoxin levels and RTC apoptosis levels [45] (Table 1).

Additionally, caspase inhibition has been shown to prevent apoptotic proximal, distal, and peritubular cell death in LPS animal models of septic AKI [16]. Cantaluppi et al. [15] have suggested a possible role for the Fas and caspase-mediated pathway in the pathogenesis of

septic AKI as well. Mitochondrial dysfunction, resulting in reduced ATP production and bioenergetic failure, is also known as an important pathogenic factor in sepsis-associated multiorgan failure, including septic AKI [32]. Mitochondrial injury in human sepsis is characterized by biochemical and structural changes, such as decreased mitochondrial mass, disruption of cristae, and extensive mitochondrial swelling [46, 47].

During combined acute cardiac and renal dysfunction, such as in sepsis, there are marked cellular and molecular changes in each organ. Septic hearts are characterized by depressed contractile function due to abnormal muscle protein expression, reduced dystrophin and altered L-type calcium currents [48, 49]. Decreased cardiac output leads to reduced renal perfusion, which further aggravates sepsis-induced AKI. Beyond the hemodynamic effects of the impaired heart on renal circulation, there are cardiac changes due to altered renal fluid balance. Indeed, endotoxin impairs glomerular filtration rate, as well as tubular function with consequent fluid and electrolyte alterations [50, 51]. Consequently, fluid overload due to AKI can lead to acute heart failure, and metabolic acidosis can impair cardiac contractility and increase heart rate, thus worsening the myocardial workload. Changes in systems physiology in the setting of sepsis can result from the systemic effects of sepsis itself, from the septic injury to "systemic pathways," or from the organ crosstalk between injured heart and kidney.

Endotoxin Removal by Extracorporeal Therapies

Endotoxin plays a pivotal role in the pathogenesis of gram-negative septic state. Based on this concept, it is reasonable to antagonize and/or to remove endotoxin when treating patients with sepsis [52, 53]. Unfortunately, clinical trials focused on antagonizing a single mediator, such as LPS, TNF-α, IL-1β, and TLR4, did not show any promising results [54].

Many studies have evaluated the clinical and biological effects of different extracorporeal blood purification techniques in sepsis, both in terms of renal support and immunomodulation. Early initiation of continuous renal replacement therapy seems to be associated with a better hemodynamic profile and outcome in septic AKI [33]. However, the timing of renal replacement therapy initiation remains heterogeneous in clinical practice and is not yet definitely supported by consistent scientific evidence.

A novel therapeutic system whereby polymyxin B is immobilized to a polystyrene-derived fiber (PMX-DHP) in a hemoperfusion device has recently been proposed in order to remove circulating endotoxin [55]. Polymyxins are cyclic cationic polypeptide antibiotics derived from *Bacillus polymyxa*. Even though both polymyxin B and colistin (polymyxin E) have good antimicrobial activity against gram-negative bacteria, their clinical use has been limited due to their nephrotoxicity and neurotoxicity [56]. However, in addition to their antimicrobial properties, polymyxins have the unusual ability to bind and neutralize endotoxin. In the 1970s, polymyxin was shown to bind lipid A, suggesting the possibility to create an affinity column able to remove endotoxin from blood passing through the system [57]. As long as polymyxin is tightly bound to the column and the endotoxin to polymyxin, the device might offer a way of taking advantage of the "anti-endotoxin" properties of polymyxin without the disadvantages of its systemic toxicity.

Animal studies opened the way to clinical trials which started in Japan, with a cartridge whereby polymyxin B is immobilized to a polystyrene-derived fiber in a hemoperfusion device able to remove circulating endotoxin [55]. The PMX cartridge is able to absorb LPS filtering blood externally with the use of an extracorporeal circuit. This relies on both the polystyrene-PMX B bonding and the LPS-PMX B affinity. The first one is the covalent linkage of PMX B to the fiber surface, thus avoiding the nephrotoxic and neurotoxic effects of PMX B. The second bond is represented by the stable interaction between lipid A and PMX B hydro-

phobic residues. Polymyxin B has also pleiotropic effects, including the entrapment of inflammatory cells, such as monocytes and neutrophils, and the clearance of cytokines TNF-α and IL-6, with a consequent reduction in the intracellular mechanisms of apoptosis.

Several trials of small cohorts of patients as well as case reports and case series reporting the efficacy of PMX-DHP in severe sepsis have been published. Cruz et al. [47] reported improved hemodynamics and oxygenation, as well as a decreased mortality, in septic patients treated with polymyxin B hemoperfusion in a systematic review and meta-analysis of 28 trials. However, the sample size of the studies was small. In 2009, in a randomized unblinded study of 64 septic patients in 10 Italian ICUs (EUPHAS-Early Use of Polymyxin Hemoperfusion in Abdominal Septic Shock), improved hemodynamics and renal function were found [46]. The EUPHAS 2 is a web-based registry of patients treated with PMX-DHP performed to validate the reproducibility of the treatment in the daily practice [58]. It is the largest registry conducted outside Japan on the clinical use of PMX-DHP in the setting of sepsis. Data analyses have confirmed the feasibility of the treatment in daily clinical practice, showing clinical benefits derived from the endotoxin removal without significant adverse events. The first randomized and controlled trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxiemia and Septic Shock – EUPHRATES) is still ongoing in the US and Canada [59].

Conclusion

Systemic gram-negative sepsis remains one of the severest conditions complicating the course of hospitalized subjects, mainly in critically ill patients. Despite significant progresses in critical care research and in molecular biology, the morbidity and mortality related to this clinical condition remain unacceptably elevated [60]. Experimental and clinical studies have suggested the presence of a detrimental crosstalk between cardiac and renal systems in the setting of sepsis, which characterizes CRS type 5. In particular, in gram-negative sepsis, the prime initiator of the process is LPS. Heart and kidney dysfunction are associated with the detrimental activity of circulating pro-inflammatory and pro-apoptotic mediators induced by LPS. Early identification of sepsis-associated AKI and heart dysfunction may improve patient clinical outcome. Moreover, new therapeutic strategies based on pharmacological agents and extracorporeal blood purification techniques have been developed, and they might represent new areas for further studies.

Statement of Ethics

No Ethics Committee approval was required.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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