REVIEW

Pulmonary Surfactant and Bacterial Lipopolysaccharide: The Interaction and its Functional Consequences

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Summary

The respiratory system is constantly exposed to pathogens which enter the lungs by inhalation or *via* blood stream. Lipopolysaccharide (LPS), also named endotoxin, can reach the airspaces as the major component of the outer membrane of Gram-negative bacteria, and lead to local inflammation and systemic toxicity. LPS affects alveolar type II (ATII) cells and pulmonary surfactant and although surfactant molecule has the effective protective mechanisms, excessive amount of LPS interacts with surfactant film and leads to its inactivation. From immunological point of view, surfactant specific proteins (SPs) SP-A and SP-D are best characterized, however, there is increasing evidence on the involvement of SP-B and SP-C and certain phospholipids in immune reactions. In animal models, the instillation of LPS to the respiratory system induces acute lung injury (ALI). It is of clinical importance that endotoxin-induced lung injury can be favorably influenced by intratracheal instillation of exogenous surfactant. The beneficial effect of this treatment was confirmed for both natural porcine and synthetic surfactants. It is believed that the surfactant preparations have anti-inflammatory properties through regulating cytokine production by inflammatory cells. The mechanism by which LPS interferes with ATII cells and surfactant layer, and its consequences are discussed below.

Key words

Lipopolysaccharide • Pulmonary surfactant • Inhibition • Alveolar type II cells • Lung injury

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Introduction

Pulmonary surfactant is a lipid-protein complex which reduces surface tension at the air/liquid interface, thereby prevents lung collapse. It is produced by the alveolar type II (ATII) cells and stored in the form of lamellar bodies (LB). After exocytosis LB are arranged into the tubular myelin that disperses into the thin film (Echaide *et al.* 2017).

About 80 % of the alveolar surfactant is phospholipids, which are at least 50 different species (Curstedt *et al.* 2013). Of these, phosphatidylcholine (PC) is about 70-80 % and dipalmitoylphosphatidylcholine (DPPC) constitutes the most important surface active component. Approximately 10 % of surfactant are neutral lipids, particularly cholesterol. Around 8-10 % of surfactant molecules form specific proteins. Hydrophilic proteins SP-A and SP-D are important for local host defense (Chroneos *et al.* 2010). Hydrophobic proteins SP-B and SP-C facilitate rapid adsorption of phospholipids at the air/liquid interface and stabilize the surfactant film during the respiratory cycle (Curstedt and Johansson 2010).

Many factors which interfere with alveolar environment are of clinical significance. The most important endogenous factors are plasma proteins entering the alveoli at increased permeability of

alveolar-capillary membrane and leading to acute respiratory distress syndrome (ARDS) (Mokra and Kosutova 2015). Oxygen treatment (Anseth *et al.* 2005, Zaher *et al.* 2007) and artificial pulmonary ventilation (de Prost and Dreyfuss 2012) are the most important exogenous factors that may impair ATII cells and pulmonary surfactant. Pulmonary surfactant can be also inactivated by meconium (Mokra and Mokry 2011), pro-inflammatory substances (de Beaufort *et al.* 2003), proteolytic enzymes or phospholipases (Holm *et al.* 1991) and bacteria (Mifsud *et al.* 2004). Complexing of lipopolysaccharide (LPS) with surfactant may contribute to the pathophysiological changes observed in some types of pneumonia (Brogden *et al.* 1986, DeLucca *et al.* 1988). Lipopolysaccharide, also termed endotoxin, is an integral part of the outer membrane of Gram-negative bacteria such as *Escherichia coli* and *Salmonella enterica*. It is composed of a hydrophilic polysaccharide (O-antigen), a core oligosaccharide and the endotoxin lipid A, a highly toxic part (Nikaido 2003). LPS possess proinflammatory activities and plays an important role in the pathogenesis of Gram-negative bacteria infection. Based on the morphology of the colonies, bacteria are identified as smooth strains expressing LPS with core oligosaccharide and O-antigen (S-LPS) or a rough strains which lack the O-antigen and can either express a complete or a truncated core oligosaccharide (Re-LPS) (Zhang *et al.* 2013). The mechanisms by which LPS interferes with ATII cells and the surfactant layer, and the consequences of this interactions are discussed below.

Lipopolysaccharide vs. phospholipid membranes interaction

Usually a simple model membranes are used to study interactions of phospholipids with various substances (Uhríková *et al.* 2004, Uhríková *et al.* 2012) including lipopolysaccharide (Cañadas *et al.* 2008, Cañadas *et al.* 2011). It was shown that Re-LPS, the minimal LPS form required for bacterial growth, interacts with DPPC films and consequently, DPPC monolayers fluidize and the surface properties change (García-Verdugo *et al.* 2007). Cañadas *et al.* (2011) evaluated the effect of the whole LPS molecule on the lung surfactant-like films composed of either DPPC or DPPC/palmitoyloleoylphosphatidylglycerol (POPG)/palmitic acid (PA) (28:9:5.6, w/w/w). As a result, already low amount of smooth LPS fluidized DPPC monolayers and prevented it to reach low surface tension during area

compression, mimicking exhalation.

Because native or animal-derived pulmonary surfactant is much more complex when it comes to phospholipid content, we studied the effect of LPS on modified porcine surfactant Curosurf® (Chiesi Farmaceutici, Parma, Italy) which is well characterized lipid-protein mixture used to treat neonatal respiratory distress syndrome. *In vitro* experiments were based on dynamic system of pulsating bubble surfactometer mimicking respiratory cycle, and optical microscopy and small- and wide-angle X-ray diffraction. Already 1 % LPS (w/w to surfactant phospholipids) prevented surfactant to reach low surface tension during area compression. LPS bound to the lipid bilayer of Curosurf® and disturbed its lamellar structure. Structural disarrangement induced by LPS was possible to restore by polymyxin B (Kolomaznik *et al.* unpublished observations). Polymyxin B is a cyclic amphipathic antibiotic which can mimic functional properties of surfactant protein B (Zaltash *et al.* 2000) and was previously shown to increase resistance of pulmonary surfactant against plasma proteins (Calkovska *et al.* 2005) and meconium (Stichtenoth *et al.* 2006).

What mechanism applies in LPS-induced surfactant inactivation? Competitive inhibition/adsorption when plasma proteins "compete" with surfactant molecules and display them from alveolar surface, is not applicable. In LPS/surfactant membrane model fluidization of surfactant film was suggested. The interaction of smooth LPS with synthetic lipid monolayers significantly fluidized these films, promoting early collapse and preventing the achievement of low surface tension. LPS exerts these fluidizing effects by acting as a „spacer“ between the lipid molecules and interfering with lipid packing upon compression (Cañadas *et al.* 2011). This mechanism has been described also in relation with lipids, mainly cholesterol (Hansen *et al.* 2015).

Lipopolysaccharide vs. surfactant proteins interaction

From an immunological point of view, the interaction of LPS with surfactant proteins is most important. **SP-A and SP-D** belong to collectins and they play an important role in the innate host defense by binding and clearing invading microbes from the lungs (Holmskov *et al.* 2003). SP-A and SP-D also influence surfactant homeostasis by regulating the surfactant

function and metabolism. In addition to binding and opsonizing pathogens, SP-A and SP-D bind to the surfaces of host defense cells, promoting or inhibiting immune cell activity through multiple cellular pathways (Kingma and Whitsett 2006). They affect the secretion of proinflammatory cytokines and products of oxidative damage (Borron *et al.* 2000), and phagocytosis of apoptotic cells (Janssen *et al.* 2008).

The structure of SP-A and SP-D is optimized for their function, the ability to recognize and bind carbohydrates on the surface of pathogens. They interact with a variety of cells including macrophages, neutrophils, eosinophils, and lymphocytes (Crouch and Wright 2001). This interaction is mediated *via* the receptor specific for lung collectin, a signal regulatory protein alpha (SIRP α), and *via* non-specific binding receptor for collectin, such as calreticulin/CD91 complex (Gardai *et al.* 2003). Membrane molecules involved in some responses to LPS, such as CD14 (Sano *et al.* 2000) or the extracellular domain of toll-like receptor 2 (TLR2) (Murakami *et al.* 2002) are also included. They affect the removal of LPS by alveolar macrophages (van Rozendaal *et al.* 1999) and remove LPS from the surfactant membrane vesicles (Kuzmenko *et al.* 2006).

SP-A and SP-D interact with different phenotypes of LPS (Crouch and Wright 2001). SP-A probably binds to a rough type LPS in calcium-dependent manner. It binds specifically to LPS lipid A, but not to the entire LPS molecule (van Iwaarden *et al.* 1994, Sano *et al.* 2000). SP-D binds to LPS through a CRD domain, especially to rough LPS by recognizing LPS inner core L-glycero-D-manno-heptose (Hep) (Wang *et al.* 2008).

Interaction of collectins with LPS suggests that they could modulate cell activation and signaling pathways after LPS challenge. SP-A reduces release of TNF- α from LPS-stimulated alveolar macrophages in rats and humans (Arias-Diaz *et al.* 2000, Gardai *et al.* 2003). *In vivo* experiments demonstrated that SP-A knock-out mice produce significantly more TNF- α than wild-type mice following intratracheal LPS administration (Borron *et al.* 2000). In contrast, SP-D moderately increases the production of TNF- α in alveolar macrophages stimulated by LPS (Bufler *et al.* 2003).

LPS increases the expression of SP-A receptors in macrophages (Chroneos and Shepherd 1995) and increases the production of SP-A and SP-D by AIII cells (McIntosh *et al.* 1996). This complex mechanism involved in the modulation of SP-A and SP-D responses to LPS is not fully understood.

The binding of SP-A and SP-D on the membrane of Gram-negative bacteria increases the permeability of the bacterial membrane. The membrane destabilization is mediated through the interaction of the collectin C-terminal domain with the membrane of LPS and explains the antimicrobial effects of these proteins (Wu *et al.* 2003). This effect was studied more in particular by Cañadas *et al.* (2008) by interaction of SP-A with rough lipopolysaccharide (Re-LPS) membranes. Permeabilization of Re-LPS membranes by SP-A is related to the extraction of LPS molecules from the membrane and creation of protein aggregates containing LPS. In addition, given that SP-A is able to bind to the lipid A moiety of LPS, and this protein is associated with the surfactant monolayer, these authors also investigated whether SP-A can minimize S-LPS effects on lung surfactant-like monolayers. SP-A was suggested to act as an LPS scavenger (Cañadas *et al.* 2011). Recently, this concept was proven by showing that SP-A/LPS interaction induces conformational changes in LPS aggregates leading to biologically less active structures (Keese *et al.* 2014).

SP-B and SP-C are extremely hydrophobic surfactant proteins. They stabilize surfactant film on the surface of the alveoli and small airways and as recently evidenced, they also have immunomodulatory properties.

Reduced expression of SP-B initiates an inflammatory response (Ikegami *et al.* 2005) and lowers the capacity of the lungs to handle LPS-induced inflammation (Epauld *et al.* 2003). The situation is similar in SP-C knock-out mice, which are susceptible to bacterial and viral infections and develop an intense inflammatory reaction (Glasser *et al.* 2009) related to the ability of SP-C to bind LPS (Garcia-Verdugo *et al.* 2009).

Detailed analysis of synthetic SP-C analogue revealed that N-terminal domain binds to the lipid A of LPS, whereas C-terminal domain of SP-C may contribute to the optimal protein conformation (Augusto *et al.* 2002). Chaby and co-workers (2005) found that CD14 binds to SP-C at place recognizing LPS. Interaction with SP-C modulates CD14 conformation, allowing for more efficient binding of LPS (Augusto *et al.* 2003). This is reminiscent to the ability of SP-A to enhance the binding of Re-LPS to CD14 (Sano *et al.* 2000). An inflammatory response is modulated by exogenous surfactant preparations containing SP-B and SP-C, and also by protein-free lipid mixtures, DPPC (Gille *et al.* 2007), phosphatidylglycerol (Numata *et al.* 2010) or some minor surfactant phospholipids (Kuronuma *et al.* 2009). From

clinical point of view, it is important that also new generation synthetic surfactants containing SP-B and SP-C analogues and synthetic phospholipids possesses anti-inflammatory features. In this respect surfactant preparation CHF5633 significantly suppressed TNF- α mRNA expression in LPS-stimulated adult monocytes, indicating its potential anti-inflammatory effects (Glaser *et al.* 2016, Glaser *et al.* 2017).

Systemic effects of LPS on lung surfactant

In living body bacterial LPS stimulates innate immunity and initiates biochemical and cellular responses leading to the local inflammation and systemic toxicity. Upon systemic intravenous or intraperitoneal administration LPS leads to hypothermia or more often to mono-, bi- or polyphasic increase in body temperature and inflammation. The intensity of response depends on the LPS serotype, the dose, the way of administration and the ambient temperature (Rudaya *et al.* 2005, Wanner *et al.* 2013). An increase in the body temperature modifies breathing pattern and contributes to respiratory instability in thermal stress (Voss *et al.* 2004). The rats with LPS-induced fever develop rapid shallow breathing with high respiratory rate and reduced tidal volume, typical for thermal tachypnea that was attributed to altered neural respiratory control (Zila *et al.* 2012). It was not known if experimentally evoked fever contributes to surfactant inactivation, and if yes, whether it is related to the body temperature, inflammation or changes in breathing pattern. Therefore, we aimed to prove the hypothesis that the changes in breathing pattern during LPS-induced fever might be related to changes in surfactant specific proteins. Indeed, experimental fever evoked the changes in all four surfactant specific proteins. Changes in proteins related to local immune mechanisms (SP-A, SP-D) are probably resulting from the systemic inflammatory response due to LPS administration. Changes in proteins related to surface activity (SP-B and SP-C) might reflect the effort of the body to stabilize the lungs during alterations of breathing pattern in thermal challenge (Kolomaznik *et al.* 2014).

At intraperitoneal administration ATII cells are not directly challenged by LPS. Therefore, stimulation of surfactant proteins release by ATII cells is probably mediated through substances which initiate signaling cascade for inflammatory mediator expression including tumor necrosis factor α (TNF- α), interleukins (IL)-1 β and IL-6, inducible nitric oxide synthase and cyclooxygenase

2, and nuclear factor (NF)- κ B (Rossol *et al.* 2011, Soares *et al.* 2012). Moreover, surfactant secretion may be influenced also by some hormones released in fever (Cameron *et al.* 2010).

Direct effect of LPS in the alveolar compartment

LPS and alveolar type II cells

The respiratory system is constantly exposed to toxic substances and pathogens from air or *via* blood stream, which can damage alveolar epithelium and lead to severe respiratory disorders. The alveolar epithelium serves as a barrier between internal and external environment and thus has a critical function in the first line defense. The alveolar epithelium consists of two morphologically different cell types – alveolar type I (ATI) cells and alveolar type II (ATII) cells. The ATII cells comprise up to 5 % of the alveolar epithelial surface area (Wong and Johnson 2013). They are responsible for reparation of alveolar epithelium upon injury and for the production of pulmonary surfactant. They also contribute to lung host defense by the secretion of antimicrobial factors (Fehrenbach 2001, Wong and Johnson 2013). In this context ATII cells have been extensively studied. ATI cells also contain toll-like receptor 4 (TLR4), a receptor for LPS and have been shown to produce the pro-inflammatory cytokines in response to LPS (Wong and Johnson 2013), but because of the close relation to pulmonary surfactant only ATII/LPS interaction is discussed below.

The LPS administration causes rapid changes in the composition of the surfactant pool and the resident cell population (Garcia-Verdugo *et al.* 2008, Wu *et al.* 2011). The response of ATII cells to microbial infection and its possible mechanisms have been studied in a variety of models, including primary cell cultures and continuous cell lines, such as human lung carcinoma type II epithelium-like A549 cells. The exposure of ATII cells to LPS modulates the levels of SPs. SP-A expression at protein and mRNA levels increased in A549 cells when they were challenged by LPS, but LPS did not affect SP-D synthesis (Chuang *et al.* 2009, Wu *et al.* 2011). This is consistent with increased SP-A gene expression in lung cells of mice exposed to inhaled LPS (George *et al.* 2003). In contrast to increased SP-A expression, expression of SP-B was reduced in ATII cells stimulated with LPS (Wang WN *et al.* 2016), consistently with experiments using an animal model of ALI resulting from

LPS exposure (Ingenito *et al.* 2001, Wang WN *et al.* 2016). It was suggested that also the amount of protein could be lower after LPS treatment. Furthermore, LPS affected expression and membrane function of SP-B by reducing interaction and stability between SP-B and lipids (Wang WN *et al.* 2016). Similarly, SP-C expression was abnormally decreased in rat ATII cells exposed to LPS (Lin *et al.* 2017).

ATII cells express functional LPS receptors like TLR2 and TLR4 (Droemann *et al.* 2003, Armstrong *et al.* 2004, MacRedmond *et al.* 2005, Wu *et al.* 2011). TLR-dependent pathway possibly explains LPS-caused pulmonary inflammation and subsequent changes in SPs expression in ATII cells. LPS specifically activates TLRs leading to activation of the NF- κ B signal transduction pathway. As a result, pro-inflammatory cytokines and chemokines such as IL-1 β , IL-6, IL-8, TNF- α and Type 1 interferons (IFN) are secreted (Slevogt *et al.* 2008, Chuang *et al.* 2009, Wu *et al.* 2011, von Schéele *et al.* 2014, Wang X *et al.* 2016).

Exposure of both, ATII cells and A549 cells to LPS reduced cell viability and induced apoptosis, typical by the formation of apoptotic bodies, cell shrinkage, DNA fragmentation, and chromatin condensation, in concentration- and time-dependent manners (Chuang *et al.* 2011, Lin *et al.* 2017). Similarly, ATII cells in animal models of LPS-induced ALI showed a significant increase in apoptosis (Kitamura *et al.* 2001). It has been reported that intratracheal instillation of a high dose of LPS in mice directly caused the death of bronchial epithelial cells (Vernooy *et al.* 2001). Moreover, mechanical ventilation as a standard therapeutic approach in the management of the ALI, may induce apoptosis of ATII cells by mechanical stretching mediated by the intrinsic mitochondrial pathway (Kuhn *et al.* 2017).

Together with apoptosis, excessive autophagic activity of ATII cells is another main cause of ALI. This type of programmed cell death is characterized by the formation of autophagosomes, degradation of cytoplasmic contents, and little chromatin condensation (Tang *et al.* 2008). Recently, Lin *et al.* (2016) found different time courses of autophagy and apoptosis in the lungs of the rats with LPS-induced ALI. At early stages (1 h and 2 h) of ALI, the mode of lung cell death started with autophagy and reached a peak at 2 h. As ALI process progressed, apoptosis was gradually increased in the lung tissue and reached its maximal level at later stages (6 h), while autophagy was time-dependently decreased. It suggests that these two types of lung cell

death might play distinct roles at different stages of LPS-induced ALI.

One of the major factors involved in LPS-induced death of alveolar epithelial cells could be an augmentation of intracellular reactive oxygen species (ROS) including increased levels of cellular nitric oxide (NO). ROS are important apoptotic factors that can cause oxidative stress and subsequent cell death (Chuang *et al.* 2011). As a ROS, NO has been implicated in the pathophysiology of ARDS in animals and humans (Kucukgul and Erdogan 2017). Previous studies showed that exposure of different cell types to LPS causes NO overproduction, subsequent cellular oxidative stress and eventually leads to cell death (Chen *et al.* 2005a, Chen *et al.* 2005b, Waak *et al.* 2009, Lee *et al.* 2010). In accordance with these studies, levels of intracellular ROS and NO were considerably increased also in A549 cells after LPS administration. Thus, LPS can directly damage alveolar epithelial cells *via* ROS-triggered apoptotic mechanism (Chuang *et al.* 2011).

The possibilities to control programmed epithelial cell death in ALI is now thoroughly investigated. Recombinant amphiregulin, a member of the epidermal growth factor family, suppressed epithelial cell apoptosis in LPS-induced lung injury in mice by inhibiting caspase-8 activity. It seems that amphiregulin signaling may be a therapeutic target for LPS-induced lung injury treatment through its prevention of epithelial cell apoptosis (Ogata-Suetsugu *et al.* 2017). Excessive autophagic activity of ATII cells in LPS-induced ALI might be suppressed by miR-34a *via* targeting autophagy-related gene FoxO3 (Song *et al.* 2017).

LPS and lung surfactant in the aveoli

Although the surfactant molecule contains effective protection mechanisms, under certain circumstances pulmonary surfactant may be damaged by excessive amounts of LPS. As mentioned above, *in vivo* LPS is a potent activator of innate immune responses and *via* TLR2 and TLR4 on the bronchial epithelium, alveolar epithelium including ATII cells and macrophages it plays crucial role in LPS-induced lung injury *in vivo* (Saito *et al.* 2005). It triggers NF- κ B-mediated production pro-inflammatory cytokines (Aul *et al.* 2012) and intratracheal administration of LPS in sufficient dose induces inflammation and tissue damage resembling ALI and ARDS (Jansson *et al.* 2004, Blumenthal *et al.* 2006). High dose LPS induces IL-1 β and TNF production leading to inflammation. Neutrophil influx into the

alveoli further worsens the lung damage by increasing pulmonary permeability, edema formation and cell death (McDonald and Usachenko 1999). Edema formation occurs 2 h after LPS administration and is dose-dependent (Jansson *et al.* 2004). All these changes can be mimicked by intratracheal administration of LPS in different animal species. Technical aspects, advantages and disadvantages of modelling of LPS-induced lung injury are reviewed e.g. in Matute-Bello *et al.* (2008).

Literature data regarding the appropriate dosage of LPS differ. In a number of studies the LPS was intratracheally administered in a wide range of 5-5,000 µg/kg of body weight (Sato *et al.* 2002, Jansson *et al.* 2004, Liu *et al.* 2013). In our pilot experiments, lung injury was induced by 100, 500 and 1,000 µg/kg in artificially ventilated rats. The animals survived 5 h ventilation with lung injury characterized with inflammation, oxidative damage lung edema, and ineffective gas exchange at 500 µg/kg of LPS. The inflammation was present not only locally, but also at the systemic level, as evidenced by the redistribution of inflammatory cells in the peripheral blood and bronchoalveolar lavage fluid (Kolomaznik *et al.* unpublished observations).

Endotoxin-induced lung injury can be favorably influenced by intratracheal instillation of exogenous surfactant. The positive effect of such treatment has been confirmed for clinically used modified porcine surfactant Curosurf® when it significantly reduced mortality in spontaneously-breathing rats with LPS-induced lung injury (van Helden *et al.* 1998). In a similar mouse model the positive effect of a synthetic surfactant based on KL4-protein was verified after 24 h (Kinniry *et al.* 2006) and the effect of natural porcine vs. synthetic surfactant

after 72 h after LPS administration was tested in rats (Mittal and Sanyal 2011). Surfactant clearly has anti-inflammatory properties, regulates the production of cytokines by inflammatory cells, but the exact mechanism of this effect is not fully understood.

Conclusions

Lipopolysaccharide interferes with all major components of pulmonary surfactant. It occurs even directly by interaction with surfactant specific proteins and incorporation into the phospholipid layers, or indirectly through alveolar type II cells. LPS-induced changes of surfactant system and their reversal can be studied *in vitro* and in different animal models. As LPS-induced lung injury is serious clinical issue, it is important to search for effective animal models to study antibiotics transfer, to develop new generation synthetic surfactants with anti-inflammatory properties and to continue in testing the exogenous surfactant preparations as drug carriers into the LPS-challenged respiratory system.

Conflict of Interest

There is no conflict of interest.

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