Antonie van Leeuwenhoek **59**: 215–223, 1991.

Mini-review

Changes in pulmonary surfactant during bacterial pneumonia

Kim A. Brogden
Respiratory Disease Research Unit, National Animal Disease Center, Agricultural Research Service, U.S. Department of Agriculture, Ames, IA 50010, USA

Received 26 September 1990; accepted 6 March 1991

Key words: bacterial pneumonia, endotoxin, lipopolysaccharide, lung, pulmonary surfactant

Abstract

In pneumonia, bacteria induce changes in pulmonary surfactant. These changes are mediated by bacteria directly on secreted surfactant or indirectly through pulmonary type II epithelial cells. The bacterial component most likely responsible is endotoxin since gram-negative bacteria more often induce these changes than gram-positive bacteria. Also, endotoxin and gram-negative bacteria induce similar changes in surfactant. The interaction of bacteria or endotoxin with secreted surfactant results in changes in the physical (i.e. density and surface tension) properties of surfactant. In addition, gram-negative bacteria or endotoxin can injure type II epithelial cells causing them to produce abnormal quantities of surfactant, abnormal concentrations of phospholipids in surfactant, and abnormal compositions (i.e. type and saturation of fatty acids) of PC. The L/S ratio, the concentration of PG, and the amount of palmitic acid in PC are all significantly lower. The changes in surfactant have a deleterious effect on lung function characterized by significant decreases in total lung capacity, static compliance, diffusing capacity, and arterial PO_2 and a significant increase in mean pulmonary arterial pressure. Also decreased concentrations of surfactant or an altered surfactant composition can result in the anatomic changes commonly seen in pneumonia such as pulmonary edema, hemorrhage, and atelectasis.

Abbreviations: BAL – Bronchoalveolar lavage, LPS – lipopolysaccharide, PC – phosphatidylcholine, PG – phosphatidylglycerol, PE – phosphatidylethanolamine, PI – phosphatidylinositol, PS – phosphatidylserine, LPC – lysophosphatidylcholine, SPH – sphingomyelin, DPPC – dipalmitoylphosphatidylcholine, L/S – lecithin/sphingomyelin

Introduction

In the lung, the alveolar epithelium is lined with an extracellular pulmonary surfactant layer (Hills 1988). This layer is the initial surface that invading bacteria contact when they enter the alveoli. As bacteria become established and interact with this layer (Reynolds 1983) as well as with epithelial cells, it is possible that surfactant metabolism, production, and function may be altered (Dobbs 1989). This hypothesis can be supported by necropsy reports in which the surface tension of BAL fluid extracted from lung tissue is abnormal in pneumonia (Sutnick & Soloff 1964; Rose & Lindberg 1968). Recently, there has been a surge in research investigating the changes in surfactant during pneumonia. This work has branched from studies on the etiology of adult respiratory distress syndrome (ARDS) since primary pulmonary infections can lead to secondary ARDS (Baughman et al. 1984).

Recent work has centered on changes in surfactant during natural or experimental pneumonia as well as the host mechanisms involved in and the bacterial factors responsible for these changes.

This mini-review is not a comprehensive review of the published literature on surfactant. The morphology (Groniowski 1983), biochemical aspects (Van Golde et al. 1988; Wright & Clements 1987; Dobbs 1989; Rooney 1985), and functional significance (Van Golde et al. 1988) of surfactant have been reviewed. Likewise, pathways for LPS induced inflammation in the lung will not be discussed here and have been reviewed elsewhere (Reynolds 1983). What follows is a summary of findings on the changes in pulmonary surfactant during bacterial pneumonia. It will first start by briefly highlighting the composition of surfactant and its role in maintaining lung homeostasis. The second section describes changes in type II pulmonary epithelial cells and surfactant during pneumonia or exposure to endotoxin in vivo. Among these are changes in the quantity of surfactant, changes in the concentration of surfactant phospholipids, and changes in the fatty acids of PC. The third section then describes the changes induced in surfactant by bacteria or endotoxin in vitro. Included are changes in the physical (i.e. density and surface tension) properties of surfactant. Finally, the relevancy of these changes and their role in the pathogenesis of pneumonia are discussed.

Composition and function of surfactant

Since surfactant exists as a layer on the epithelial surface, it can be easily obtained by lavage of the lungs with saline. The surfactant is then separated from alveolar cells and contaminating proteins by differential and density gradient centrifugation (Possmayer et al. 1984; Van Golde et al. 1988). In this form, surfactant is chemically heterogeneous (Dobbs 1989; Van Golde et al. 1988) and exists as small, unilamellar and large, multilamellar vesicles (Brogden et al. 1986a; Magoon et al. 1983). Tubular myelin is also present (Magoon et al. 1983).

Surfactant is predominately lipid (80–90%) with several specific proteins (10%) and small amounts of carbohydrate (Dobbs 1989; Van Golde et al. 1988). The lipids, extracted with chloroform and methanol, contain approximately 80% phospholipids and approximately 20% neutral lipids such as cholesterol, cholesterol esters, di- and tri- acylglycerols, and some free fatty acids (Possmayer et al. 1984). The distribution of phospholipids in surfactant is similar among a large number of animals but species specific differences do occur (Shelley et al. 1984; Jobe et al. 1980). Generally, surfactant phospholipids contain 67–80% PC, 4–10% PG, 3–10% PE, 3–6% PI, 0.5–2.5% PS, 1–6% LPC, and 1–8% SPH. Approximately 50–60% of the PC contain saturated palmitic acid and is DPPC (Rooney 1985; Van Golde et al. 1988).

Surfactant also has 3 families of associated proteins, which are referred to as SP-A, SP-B, and SP-C (Possmayer 1988). SP-A (35 kDa) is the major protein associated with surfactant. This protein shares sequence identity with lectins and is thought to bind carbohydrate from type II epithelial cells, to induce lipid aggregation as tubular myelin, and to function as an endocrine factor to regulate the amount of surfactant in the alveolus. The two other proteins, SP-B (7 kDa) and SP-C (5 kDa) are extremely hydrophobic. Both facilitate the adsorption and spreading of DPPC at the air-liquid interface.

Surfactant works by forming a layer at the interface between the epithelium and the air within the alveoli (Hills 1988). This prevents the development of a water-air interface which would have 2 to 14 times the surface tension of the surfactant-air interface. This layer maintains alveolar stability by providing a stable, low surface tension (Dobbs 1989; Possmayer et al. 1984; Van Golde et al. 1988) and maintaining lung surface elasticity (Clements & Tierney 1965). The low surface tension functions to reduce the effort of breathing, protect the lungs against collapse at end expiration (Van Golde et al. 1988) and prevent transudation of serous fluid from the capillaries into the airspaces (Van Golde et al. 1988).

Each component in surfactant is necessary for its overall function. The DPPC provides both the stability and low surface tension to surfactant (Dobbs 1989). Unsaturated PC aids in rapid adsorption of

surfactant to epithelial cells. Unsaturated PC and other phospholipids promote rapid spreading of surfactant across the air-liquid interface (Dobbs 1989; Possmayer et al. 1984). Surfactant proteins, SP-B and SP-C, facilitate the adsorption and spreading of DPPC. Addition of SP-A further enhances the surface activity effects of SP-B and SP-C.

Changes in surfactant in vivo during pneumonia or experimental infections

Initially, some anatomic changes in the lung during pneumonia (i.e. atelectasis) were correlated with decreases in the amount and surface activity of surfactant in extracts of infected tissue (Sutnick & Soloff 1964). Some factor from the infecting organism was thought to be responsible for the loss of surface activity by either destroying surfactant or by acting as an antagonist in its function. Similarly, Clements & Tierney (1965), postulated that abnormalities of surfactant may be anticipated in certain respiratory diseases if subjacent epithelial cells were injured or if the epithelial cell surface was contaminated by substances which interact with the surfactant layer. The loss of surface activity in the areas contiguous to those infected was thought to result in atelectasis and represent an etiologic factor in the pathogenesis of pneumonia (Rose & Lindberg 1968).

It is now generally accepted that changes in surfactant occur in pulmonary bacterial infections. First, an increase in the surface tension of surfactant has been observed. For example, Sutnick & Soloff (1964) reported that lung extracts from patients who died of pneumonia had a significantly higher surface tension of 19.7 dynes/cm at minimum compression on a Langmuir-Wilhelmy balance. These extracts had a narrow hysteresis loop with an average difference of 8.0 dynes/cm between cycles. In contrast, the lung extracts from patients without pneumonia had a surface tension of 5.8 dynes/cm and had a wide hysteresis loop with an average difference of 24.7 dynes/cm between cycles. Similar increases in surface tension of surfactant can be reproduced experimentally in animals by inducing pneumonia (Von Wichert & Wilke 1976) or after endotracheal injection of endotoxin (Tahvanainen & Hallman 1987).

Second, a decrease in the quantity of surfactant has been observed during pneumonia (Rose & Lindberg 1968) or after experimental deposition of endotoxin into the lungs of animals. In the latter, Shimizu et al. (1976) observed a significant decrease in the amount of total lipids and total phospholipids from BAL fluid of endotoxin treated rabbits. Tahvanainen and Hallman (1987) observed a 52–67% decrease in surfactant phospholipids from guinea pigs after endotracheal injection of endotoxin.

Finally, a shift in the concentration of phospholipids of surfactant and composition of fatty acids in PC has been observed during pneumonia or after experimental deposition of endotoxin in animals. The shift in the concentration of phospholipids is characterized by a decrease in the concentration of PC and PG and an increase in the concentration of SPH. When the shift in phospholipids is expressed as a ratio, it becomes a good indicator of bacterial lung infection. One useful ratio is the concentration of PC to SPH often referred to as the L/S ratio. Hallman et al. (1982) observed a L/S ratio of 6.65 in patients with pneumonia and a ratio of 19.73 in patients without pneumonia. A similar trend occurs in animals exposed to endotoxin (Shimizu et al. 1976). Tahvanainen & Hallman (1987) found the L/S ratio in BAL fluids of guinea pigs after endotoxin induced lung injury was 9.2 for those exposed to endotoxin and 32.5 for controls. PG and PI share a common synthetic pathway and a shift in one results in a proportional change in the other. Ratios of PG/PI, PC/PI, or PC/PG can also be useful indicators phospholipid concentration shifts. King et al. (1989) showed a decrease in the PG/PI ratio of BAL fluid of baboons exposed to 80% oxygen plus *Pseudomonas aeruginosa* to 27% of the control group. Likewise, Sachse (1989) showed a significant decrease in PC/PI and PC/PG ratios in BAL fluids of pigs after experimental infection with *Pasteurella multocida*.

In addition to the shift in the concentration of phospholipids in surfactant during pneumonia, changes have also been described in the fatty acids

of PC. Generally, this change is characterized by a decrease in the amount of palmitic acid (Baughman et al. 1984; Shimizu et al. 1976). However, changes also occur in stearic acid (Baughman et al. 1984; Shimizu et al. 1976), oleic acid (Baughman et al. 1984), linoleic acid (Baughman et al. 1984) and arachidonic acid (Shimizu et al. 1976). The changes are consistent enough to differentiate between normal individuals and those with pneumonia. A ratio of palmitic to oleic acid of 1.0 (SD 2.7) was shown to be significantly lower in individuals with pneumonia than the ratio of 3.4 (SD 1.10) in individuals without pneumonia (Baughman et al. 1984).

Changes in type II epithelial cells

In gram-negative bacterial pneumonia, an increase in type II and interstitial cells occur with a decrease in type I and endothelial cells (Coalson et al. 1989). The type II cells often have a significant increase in cell volume, increase in cytoplasmic organelles, and aberrations in the lamellar bodies. Similar results were reported earlier by Lopez et al. (1987) after intratracheal inoculation of LPS in rats. Specifically, LPS inoculation resulted in significant increases in type II cell size (27–56%). Lamellar bodies were also 12 to 15% of cell size. Based on all of these findings, Coalson et al. (1989) felt that changes in surfactant are due to perturbations in type II cell function rather than as a secondary aspect of nonselective cellular destruction and fluid transudation. By using isolated, viable type II cells, Arcil et al. (1985) was able to show that *Escherichia coli* LPS binds to the cell membrane and induces a modification of ion permeability and fluidity of the cell membrane. These modifications were characterized by an increase in the uptake of labelled Ca^{+2} and increase in fluorescence polarization with a 1,6-diphenyl-1,3,5-hexatriene probe.

Changes induced in surfactant in vitro

Early on, the increase in surface tension of BAL fluid from individuals with pneumonia was thought to result from the interaction of bacteria or their toxins with the surfactant layer (Clements & Tierney 1965; Sutnick & Soloff 1964). To show this, Rose et al. (1968) incubated different clinical bacterial isolates with rabbit surfactant and measured the surface tension. Gram-negative bacteria (particularly *Aerobacter aerogenes, Pseudomonas aeruginosa, Proteus species,* and *Klebsiella pneumoniae*) significantly increased the surface tension of surfactant whereas gram-positive bacteria did not.

The difference in the outer surface of Gram-negative bacteria might account for their ability to increase the surface tension of surfactant. The component most likely responsible is endotoxin. Endotoxin, a constituent unique to the outer surface of gram-negative bacteria, contains LPS, protein, and lipid. Incubation of LPS with surfactant increases the density of surfactant (Brogden et al. 1986a, b; DeLucca et al. 1988). For example, in a 1.02–1.12 gm/ml sucrose gradient, surfactant buoys at a density of 1.050–1.060 gm/ml (Fig. 1; tube a). *Escherichia coli* 026 : B6 LPS forms a pellet (Fig. 1: tube c). However, when surfactant and *E. coli* LPS are combined, surfactant then buoys at a density of 1.06–1.08 gm/ml (Fig. 1; tube b). This is a result of LPS complexing with the surfactant vesicles as demonstrated by immunoelectron microscopy (Brogden et al. 1986a).

Incubation of LPS with surfactant also increases the surface tension of surfactant (Delucca et al. 1988; Brogden et al. 1989). Similar results are shown in Table 1 as determined with a surface tensiometer (Barrow & Hills 1979) and a goniometer (Cotton & Hills 1984). Both the surface tension and contact angles of surfactant are consistently higher after incubation with LPS. In some instances, LPS (i.e. *P. aeruginosa* LPS) completely destroys the surface activity of surfactant and the surface tension of the mixture is almost as high as the surface tension of the LPS alone. This change can also be demonstrated in a Langmuir trough with a Wilhelmy balance (Brogden & Hills 1986). Surfactant has a wide hysteresis loop with a surface tension of 10 dynes/cm at compression to 20% of the trough and a difference of 15 dynes/cm between mid compression and mid expansion (Fig. 2). In contrast, LPS + surfactant has a higher surface tension of 25 dynes/cm and a narrower hysteresis

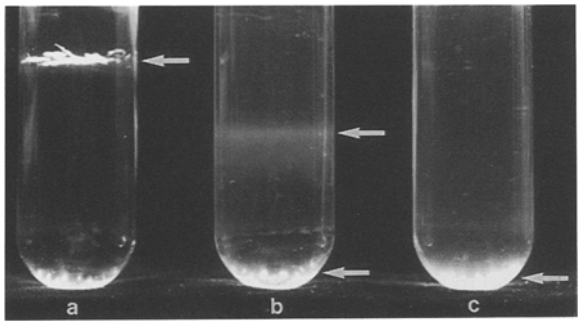

Fig. 1. The increase in density of surfactant induced after incubation with *Escherichia coli* LPS. Shown is (a) the band of surfactant at a density of 1.05–1.06 gm/ml, (b) the band of surfactant after incubation with *E. coli* LPS at a density of 1.06–1.08 gm/ml, and (c) *E. coli* LPS at a density > 1.12 gm/ml.

loop with a difference of 10 dynes/cm. LPS alone has a high surface tension and a minimal hysteresis loop with a difference of less than 5 dynes/cm between mid compression and mid expansion.

In addition to LPS, only a few other bacterial components have been reported to interact with surfactant. McArthur & Ceri (1983) reported a lectin reaction between *P. aeruginosa* polysaccharides and surfactant (probably a result of the Ca^{++} dependent, mannose binding properties of SP-A) that may represent an adhesion mechanism important in lung colonization. Similarly, Brogden et al. (1989) showed that the capsular polysaccharide of *P. haemolytica* precipitated with surfactant. This precipitation also appeared to be a lectin-carbohydrate reaction of the →3)-0-(2-acetamido-2-deoxy-4-0-acetyl-β-D-mannopyranosyluronic acid)-(1→ 4)-0-(2-acetamido-2-deoxy-β-D-mannopyranose)-(1→ structure with SP-A. Incubation of capsular polysaccharide with surfactant only increased the density of surfactant and not the surface tension of surfactant. Other bacterial toxins and enzymes have been thought to be involved in surfactant destruction during infection (Clements & Tierney 1965). It is possible that bacterial proteinases or phospholipases may degrade surfactant during pneumonia but there is no documented evidence of this.

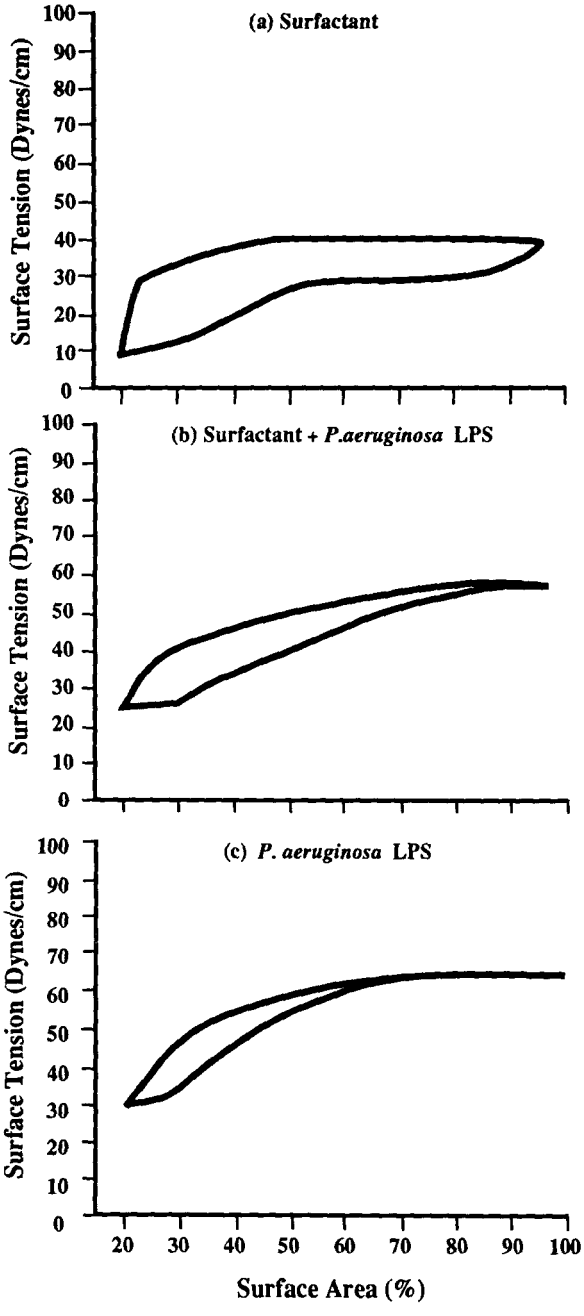

Fig. 2. The change in the hysteresis loops in a Langmuir-Wilhelmy balance induced in surfactant after incubation with *Pseudomonas aeruginosa* LPS. Shown is the hysteresis loops of (a) surfactant, (b) surfactant after incubation with *P. aeruginosa* LPS, and (c) *P. aeruginosa* LPS.

Consequences of surfactant impairment

The results from studies sited in this review clearly show that 2 main changes occur in surfactant during

both natural and experimentally induced pneumonia. One change is characterized by an increase in the surface tension induced by surfactant. This is a consistent finding and can easily be reproduced in vitro by mixing surfactant with gram-negative bacteria or LPS. The other change is the decrease in the quantity and quality of surfactant. Total surfactant, the L/S ratio, the concentration of PG, and the amount of palmitic acid in PC are all significantly lower. Both of these changes play a role in the elasticity and mechanical behavior of the lungs as well as lung function. Any increase in surface tension due to an altered surfactant, abnormal quantity of surfactant, or abnormal concentration of surfactant constituents will have a deleterious effect on lung function. These include decreases in total lung capacity, static compliance, diffusing capacity, and arterial PO_2 (Coalson et al. 1989). Also, anatomic changes, such as pulmonary edema (Albert et al. 1979), hemorrhage, and atelectasis (Clements & Tierney 1965; Sutnick & Soloff 1964) can be seen.

Initially the changes in surface tension observed in BAL fluids from individuals with bacterial pneumonia were thought to be due to interaction of surfactant with edema fluid. In fact, the surface activity of surfactant is destroyed when it is mixed with relatively large quantities of plasma and interstitial protein (Holm et al. 1985). However, this is only secondary to initial changes of bacterial infection and the following sequence probably occurs (Fig. 3). Bacteria entering the alveoli first come in contact with the surfactant layer. The secreted endotoxin interacts with surfactant increasing its surface tension (Rose & Lindberg 1968; Brogden et al. 1986a). The altered surface tension may lead to the collapse of surrounding alveoli thus initiating the transudation of fluid from the capillaries. The influx of plasma proteins then compounds the destruction of the surface activity of surfactant as proposed by Holm et al. (1985).

The decrease in the quantity of surfactant and the shift in the composition of surfactant may then result from endotoxin injury to the type II cell by either of two mechanisms. LPS may attach directly to the type II cell influencing the functional properties of these cells and their membranes (Aracil et al. 1985) or inducing cell death by complement mediated pathways. Bosch et al. (1990) observed that lungs from endotoxin treated rats yielded a lower number (65%) of type II cells than control animals. These cells were also less viable (70% as compared to 90% in control animals). Obviously, LPS-induced cytotoxicity would affect the quantity of surfactant produced. More likely LPS, in sublethal concentrations, complexes with surfactant and

Table 1. Comparison of the surface tension and contact angle of LPS and surfactant mixtures.

Preparation	Surface tension (dynes/cm)	Contact angles (°)
Surfactant	31.4 ± 0.2[a]	36
Surfactant + *E. agglomerans* LPS[b]	34.4 ± 0.4	57
E. agglomerans LPS[b]	73.8 ± 0.1	68
Surfactant + *P. haemolytica* LPS[c]	57.7 ± 0.4	ND[d]
P. haemolytica LPS[c]	73.4 ± 0.1	ND
Surfactant + *S. typhi* LPS	53.4 ± 0.6	53
S. typhi LPS	72.4 ± 0.2	65
Surfactant + *K. pneumoniae* LPS	58.3 ± 0.3	62
K. pneumoniae LPS	69.6 ± 0.2	67
Surfactant + *P. multocida* LPS	57.7 ± 0.1	61
P. multocida LPS	73.1 ± 0.1	66
Surfactant + *P. aeruginosa* LPS	64.8 ± 0.2	66
P. aeruginosa LPS	67.5 ± 0.1	68
0.025 M Tris Buffer (pH 7.2)	74.3 ± 0.1	65

[a] Mean ± standard error of 10 replications.
[b] DeLucca et al. 1988 [c] Brogden et al. 1989 [d] ND = not done

is taken up as part of the normal reutilization of surfactant phospholipids. Surfactant constituents are recycled between the alveolar layer and the surfactant-storing lamellar bodies in the type II cells (Kalina & Socher 1990). Studies with isolated type II cells indicate that PC is taken up by the cell, degraded in the lysosomes, and transferred to the endoplasmic reticulum for reutilization. (Van Golde et al. 1988). LPS attached to surfactant would gain entrance to the cell and induce alterations in phospholipid metabolism that would affect the amount of surfactant produced.

Shifts in the concentration of phospholipids in surfactant is a result of alterations in the phospholipid synthesis pathways. It appears now that this is not due to plasma lipid contamination. BAL fluids contain phospholipids that are found only in trace amounts in plasma (Hallman et al. 1982). It is, however, probably a result of LPS-induced alterations in phospholipid metabolism. The effect of LPS on PC metabolism of type II cells was examined by Bosch et al. (1990) to explain the depression of pulmonary PC synthesis. The level of (^{14}C) choline incorporated into PC from cells of endotoxin treated rats was decreased by 50% when compared with the level of (^{14}C) choline incorporated into PC from cells of control rats. Besides a depression in PC synthesis, LPS has been shown to stimulate a sustained degradation of PC in peritoneal macrophages via induction of a specific phospholipase (Grove et al. 1990). If such a mechanism occurs in type II cells or alveolar macrophages, it would help explain the decrease in PC reported in BAL of individuals with pneumonia. The changes in PI and PG may be related to changes in their synthetic pathways. They both share a common precursor within the surfactant synthesis pathway, and a reciprocal relationship between the concentrations of these components may occur.

The specific mechanisms for the alteration in the type and composition of fatty acids in PC during acute pneumonia are not known. The changes are not due to plasma lipid contamination because Baughman et al. (1984) found that the proportions of linoleic acid in plasma changed little in BAL fluid from patients with pneumonia. The differences in surfactant phospholipid fatty acid composition between patients with and without pneumonia may reflect to some extent a similar common metabolic pathway. This is demonstrated by an inverse relationship between concentrations of palmitic acid and oleic acid. Baughman et al. (1984) reported low concentrations of palmitic acid and high concentrations of oleic acid in surfactant of patients with pneumonia whereas the reverse is true in surfactant from patients without pneumonia. Whether the shift is a result of a metabolic pathway change during surfactant synthesis or a result of interaction of surfactant with neutrophils or bacteria is yet to be determined.

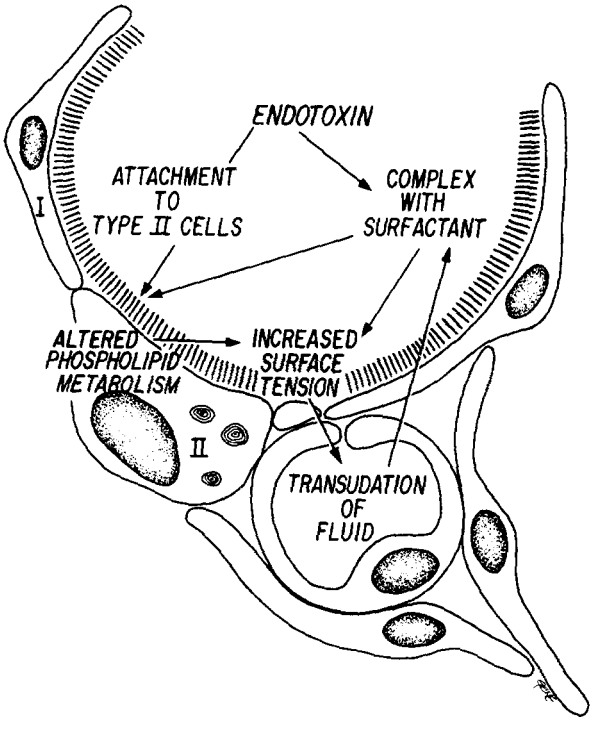

Fig. 3. A diagram illustrating the changes that can occur in pulmonary surfactant during bacterial pneumonia. Bacteria entering the alveoli first come in contact with the surfactant layer. The secreted endotoxin complexes with surfactant increasing its surface tension. This leads to the transudation of fluid from the capillaries. The influx of plasma proteins then compounds the destruction of the surface activity of surfactant. Alternately, endotoxin may attach directly to the type II cell influencing the functional properties of these cells and their membranes. This results in an altered phospholipid metabolism that also affects the quantity and quality of surfactant produced.

References

Albert RK, Lakshminarayan S, Hildebrandt J, Kirk W & Butler J (1979) Increased surface tension favors pulmonary edema formation in anesthetized dogs' lungs. J. Clin. Invest. 63: 1015–1018

Aracil FM, Bosch MA & Municio AM (1985) Influence of E. coli lipopolysaccharide binding to rat alveolar Type II cells on their functional properties. Molec. Cellular Biochem. 68: 59–66

Barrow RE & Hills BA (1979) A critical assessment of the Wilnelmy method in studying lung surfactants. J. Physiol. 295: 217–227

Baughman RP, Stein E, MacGee J, Rashkin M & Sahebjami H (1984) Changes in fatty acids in phospholipids of the bronchoalveolar fluid in bacterial pneumonia and in adult respiratory distress syndrome. Clin. Chem. 30: 521–523

Bosch MA, Risco C & Martin-Municio A (1990) Effect of Escherichia coli lipopolysaccharide on phosphatidylcholine biosynthesis by rat lung and alveolar type II cells. Mol. Cel. Biochem. 93: 167–172

Brogden KA, Cutlip RC & Lehmkuhl HD (1986a) Complexing of bacterial lipopolysaccharide with lung surfactant. Infect. Immun. 52: 644–649

Brogden KA & Hills BA (1986) Surface tension properties of pulmonary surfactant and lipopolysaccharide mixtures. Proceedings XIV International Congress of Microbiology, Manchester, England. (p 64)

Brogden KA, Rimler RB, Cutlip RC, Lehmkuhl HD (1986b) Incubation of Pasteurella haemolytica and Pasteurella multocida lipopolysaccharide with sheep lung surfactant. Am. J. Vet. Res. 47: 727–729

Brogden KA, Adlam C, Lehmkuhl HD, Cutlip RC, Knights JM & Engen RL (1989) Effect of Pasteurella haemolytica (A1) capsular polysaccharide on sheep lung in vivo and on pulmonary surfactant in vitro. Am. J. Vet. Res. 50: 555–5591

Clements JA & Tierney DF (1965) Alveolar instability associated with altered surface tension. In: Fenn WO & Rahn H (Ed) Respiration (pp 1565–1583) American Physiological Society, Washington, DC

Coalson JJ, King RJ, Winter VT, Prihoda TJ, Anzueto AR, Peters JI & Johanson WG Jr (1989) O_2- and pneumonia-induced lung injury I. Pathological and morphometric studies. J. Appl. Physiol. 67: 346–356

Cotton DB & Hills BA (1984) Pulmonary surfactant: Hydorphobic nature of the mucosal surface of the human amnion. J. Physiol. 349: 411–418

DeLucca AJ II, Brogden KA & Engen R (1988) Enterobacter agglomerans lipopolysaccharide-induced changes in pulmonary surfactant as a factor in the pathogenesis of Byssinosis. J. Clin. Microbiol. 26: 778–780

Dobbs LG (1989) Pulmonary surfactant. Ann. Rev. Med. 40: 431–436

Groniowski JA (1983) Fine structural basis of pulmonary surfactant. Inter. Rev. Exper. Path. 25: 183–238

Hallman M, Spragg R, Harrell JH, Moser KM & Gluck L (1982) Evidence of lung surfactant abnormality in respiratory failure. Study of bronchoalveolar lavage phospholipids, surface activity, phospholipase activity, and plasma myoinositol. J. Clin. Invest. 70: 673–683

Hallman M, Arjomaa P, Tahvanainen J, Lachmann B & Spragg R (1985) Endobronchial surface active phospholipids in various pulmonary diseases. Eur. J. Resp. Dis. Suppl. 142: 37–47

Hills BA (1988) The Biology of Surfactant. Cambridge University Press, Cambridge

Holm BA, Notter RH & Finkelstein JN (1985) Surface property changes from interactions of albumin with natural lung surfactant and extracted lung lipids. Chem. Phys. Lipids 38: 287–298

Jobe A, Ikegami M, Sarton-Miller I & Barajas L (1980) Surfactant metabolism of newborn lamb lungs studied in vivo. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 49: 1091–1098

Kalina M & Socher R (1990) Internalization of pulmonary surfactant into lamellar bodies of cultured rat pulmonary type II cells. J. Histochem. Cytochem. 38: 483–492

King RJ, Coalson JJ, Seidenfeld JJ, Anzueto AR, Smith DB & Peters JI (1989) O_2- and pneumonia-induced lung injury. II. Properties of pulmonary surfactant. J. Appl. Physiol. 67: 357–365

Lopez A, Albassam M, Yong S, Sharma A, Lillie LE & Prior MG (1987) Profiles of Type-II pneumocytes in rats inoculated intratracheally with bacterial lipopolysaccharide. Am. J. Vet. Res. 10: 1534–1539

McArthur HAI & Ceri H (1983) Interaction of a rat lung lectin with the polysaccharides of Pseudomonas aeruginosa. Infect. Immun. 42: 574–578

Magoon MW, Wright JR, Baritussio A, Williams MC, Goerke J, Benson BJ, Hamilton RL & Clements JA (1983) Subfractionation of lung surfactant. Implications for metabolism and surface activity. Biochim. Biophys. Acta 750: 18–31

Possmayer F, Yu SH, Weber JM & Harding PGR (1984) Pulmonary surfactant. Can. J. Biochem. Cell Biol. 62: 1121–1133

Possmayer F (1988) A proposed nomenclature for pulmonary surfactant-associated proteins. Am. Rev. Respir. Dis. 138: 990–998

Reynolds HY (1983) Lung Inflammation: Rode of endogenous chemotactic factors in attracting polymorphonuclear granulocytes. Am. Rev. Respir. Dis. 127: S16–S25

Rooney SA (1985) The surfactant system and lung phospholipid biochemistry. Am. Rev. Respir. Dis. 131: 439–460

Rooney SA (1984) Lung surfactant. Environ. Health Perspectives 55: 205–226

Rose M & Lindberg DAB (1968) Effect of pulmonary pathogens on surfactant. Diseases of the Chest 53: 541–544

Sachse K (1989) Changes in the relative concentrations of surfactant phospholipids in young pigs with experimental pneumonia. J. Vet. Med. 36: 385–390

Shelley SA, Paciga JE & Balis JU (1984) Lung surfactant phospholipids in different animal species. Lipids 19: 857–862

Shimizu CSN & Mahour GH (1976) Effect of endotoxins on rabbit alveolar phospholipids. J. Surgical Res. 20: 25–32

Sutnick AI & Soloff LA (1964) Atelectasis with pneumonia. A pathophysiologic study. Ann. Internal Med. 60: 39–46

Tahvanainen J & Hallman M (1987) Surfactant abnormality after endotoxin-induced lung injury in guinea-pigs. Eur. J. Respir. Dis. 71: 250–258

Van Golde LMG, Batenburg JJ & Robertson B (1988) The pulmonary surfactant system: Biochemical aspects and functional significance. Physiol. Rev. 68: 374–455

Von Wichert PV & Wilke A (1976) Alveolar stability and phospholipid content in normal pig lungs and in pig lungs with mycoplasma pneumonia. Scand. J. Resp. Dis. 57: 25–30

Wright JR & Clements JA (1987) Metabolism and turnover of lung surfactant. Am. Rev. Respir. Dis. 135: 426–444