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Forum Review

Regulation of Surfactant Protein Gene Expression by Hyperoxia in the Lung

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ABSTRACT

Pulmonary surfactant, a complex of lipids and proteins, maintains alveolar integrity and participates in the control of host defense and inflammation in the lung. Surfactant proteins A, B, C, and D are important components of surfactant that play diverse roles in the surface tension reducing as well as host defense and inflammation control functions of surfactant. Hyperoxia or exposure of cells/tissues to elevated levels of oxygen occurs when high levels of oxygen are used to treat a variety of pulmonary disorders that include respiratory distress syndrome of premature infants, emphysema, sarcoidosis, end-stage lung diseases, and others. The lung serves as a primary target organ in hyperoxia, and hyperoxic lung injury is characterized by pulmonary edema, inflammation, and respiratory failure. Hyperoxic lung injury is associated with significant changes in the expression of surfactant proteins that likely serves as an adaptive response to elevated oxygen levels. In most animal species studied, hyperoxia increases the tissue expression of surfactant protein mRNAs. A limited number of studies have indicated that the increased tissue expression of surfactant protein mRNAs is associated with increased levels of surfactant proteins in the bronchoalveolar lavage. *Antioxid. Redox Signal.* 6, 185–190.

INTRODUCTION

THE HUMAN LUNG contains approximately 300 million alveoli that facilitate gas exchange between inhaled air and the venous blood to maintain respiration (41). Because of the critical roles that the alveoli perform, it is essential to maintain the integrity of the alveoli during respiration. Any perturbations that weaken the stability of the alveoli will lead to collapse of the lung, resulting in respiratory distress and possible death. The stability of the alveoli during the respiratory cycle is maintained by surfactant (20), a lipoprotein complex that is synthesized and secreted by the alveolar type II epithelial cells. Surfactant stabilizes the alveoli by counteracting contractile forces on the alveolar surface to reduce surface tension during respiration. Apart from reducing surface tension, surfactant also plays important roles in the control of host defense and inflammation in the lung (17).

Surfactant is a mixture of phospholipids and proteins that is composed of 90% lipids and 10% proteins by weight (15). Phospholipids comprise 95% of the lipid content of surfactant of which phosphatidylcholine constitutes 70–80%. The majority of the phosphatidylcholine is present in the form of dipalmitoylphosphatidylcholine (DPPC). Several distinct lung-specific proteins form the protein content of surfactant: surfactant protein (SP)-A, B, C, and D. SP-A and SP-D are hydrophilic proteins that are members of the collectin family of proteins (21). SP-A and SP-D are characterized by an amino-terminal collagen-like domain and a lectin-like carboxy-terminus. SP-A and SP-D are thought to play important roles in the control of host defense and inflammation in the lung. SP-B and SP-C are highly hydrophobic proteins that appear to play a more direct role in influencing the surface tension-reducing properties of surfactant (40). Deficiency of surfactant proteins, particularly SP-B, results in the loss of surfactant

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function leading to respiratory failure (13, 36). Deficiency of surfactant as a result of premature birth is directly linked to the development of newborn respiratory distress syndrome (9), the leading cause of neonatal morbidity and mortality in developed nations.

Surfactant synthesis is subject to developmental and multifactorial regulation in the lung (31). The synthesis of surfactant lipids and proteins is augmented during the final 15–20% of gestation in most mammals, with the maximum synthesis occurring just prior to birth. Adequate levels of surfactant are necessary for the successful transition of the fetus from an intrauterine environment to an air-breathing environment. The production of surfactant and antioxidant enzymes is induced to peak levels during the final stages of gestation prior to birth. Peak levels of surfactant and antioxidants ensure protection to the lung during transition from a low-oxygen intrauterine environment to the oxygen-rich environment of atmospheric air.

Hyperoxia or exposure of cells/tissues to elevated levels of oxygen is encountered in clinical settings when high levels of oxygen are used to treat a variety of pulmonary disorders that include respiratory distress syndrome of premature infants, emphysema, sarcoidosis, end-stage lung diseases, and others. Hyperbaric oxygen therapy is currently being used to treat infections, wound healing, migraine, brain injuries, chronic fatigue syndrome, and others. Due to its ready accessibility to the outside environment and large surface area, the lung is a primary target for oxygen mediated changes in hyperoxia. Hyperoxic lung injury in neonates and adults is characterized by pulmonary edema, inflammation, and respiratory failure (14, 16, 19). Newborn infants, particularly premature infants, are at risk of developing lung injury as a result of underdeveloped lung and deficiency of surfactant. The biochemical and molecular bases of lung injury in hyperoxia are not completely understood. Hyperoxic lung injury is associated with significant changes in gene expression indicating that alterations in gene expression, contribute to tissue injury.

HYPEROXIA REGULATION OF SURFACTANT PHOSPHOLIPID SYNTHESIS

It has become clear that, in addition to antioxidant systems, other stress-induced proteins and responses play important roles in adaptation to hyperoxia. Alterations in pulmonary surfactant levels could be one of the critical steps that occur in response to elevated oxygen levels. In most animals, hyperoxic lung injury is characterized by pulmonary edema, increased permeability to solute and protein, and decreased dynamic surface activity of surfactant. The effects of hyperoxia on surfactant lipid content and lipid species appear to vary depending on the animal species. In rabbits (22) and baboons (26) exposed to 100% O_2 for 64 and 96 h, respectively, surfactant phospholipid content was decreased. The dynamic surface activity of surfactant was also impaired. Alveolar type II cells isolated from adult rabbits exposed to 100% O_2 for 64 h showed a 60% decrease in phosphatidylcholine synthesis, cellular lipid content, and the specific activity of glycerol 3-phosphate acyltransferase (24). All these parameters were restored to normal levels during the recovery phase and increased significantly above normal levels after 3 days postexposure.

In adult rats (11) and hamsters (33) exposed to 100% O_2 for 64 h and 8 days, respectively, surfactant levels, as determined by the phospholipid content of lung lavage, increased by two- to threefold. The phospholipid composition of surfactant was also altered; whereas in rats the percentage of DPPC, the principal surface-active phospholipid, decreased, it increased in hamsters. In all species, phosphatidylglycerd/phosphatidylinositol ratios decreased in hyperoxia and may therefore serve as a predictor of lung injury. Chronic exposure of rabbits to sublethal (60%) oxygen concentrations did not alter several indicators of lung injury, such as lung compliance and alveolar permeability to solute and alveolar protein levels, as compared with control animals (23). The levels of phospholipids in alveolar lavage were significantly increased, and this was reflected in the biosynthetic activity of isolated alveolar type II cells to synthesize phosphatidylcholine.

Exogenous administration of surfactant to rabbits significantly decreased the progression of hyperoxic injury by increasing alveolar phospholipid levels and total lung capacity. Surfactant-treated animals also had significantly lower amounts of alveolar protein, and lung atelectasis was reduced (29, 30).

HYPEROXIA REGULATION OF SURFACTANT PROTEIN GENE EXPRESSION

In association with the changes in the levels of surfactant lipids, alterations in the expression of surfactant protein genes occur in hyperoxia. Again, as in the case of surfactant lipids, the effects of hyperoxia on surfactant protein gene expression vary depending on the animal species (Table 1).

Regulation in adult animals

Exposure of adult rats continuously to 85% O_2 for up to 7 days increased the lavage content of SP-A, SP-B, and SP-C in a time-dependent manner (34, 35). After 5 days of exposure, SP-A, SP-B, and SP-C protein levels in lavage were increased by greater than fivefold compared with control animals that were exposed to room air. The increases in the content of SP-A, SP-B, and SP-C proteins were associated with similar increases in the expression of mRNAs, indicating that the effects of hyperoxia on surfactant protein gene expression are exerted at the pretranslational level (34, 35). In alveolar type II cells isolated from hyperoxia-exposed rats, SP-A secretion and synthesis increased by seven- and twofold, respectively, suggesting that increased SP-A gene expression must be due in part to an effect on type II cells (34). In adult rabbits exposed to 100% O_2 for 64 h, SP-A and SP-B but not SP-C mRNA expression in the lung increased significantly compared with expression in animals exposed to room air (25). *In situ* hybridization analysis showed that hyperoxia had a much greater effect on the expression of SP-A and SP-B mRNAs in Clara cells than in alveolar type II cells; SP-A and SP-B mRNA expression increased by 20-fold in Clara cells, whereas their expression increased by only twofold in type cells (25). The expression levels of SP-A and SP-B mRNAs are considerably lower in Clara cells compared with alveolar type II cells and might explain the rather significant inductive effects of hyperoxia on SP-A and SP-B expression in Clara cells.

TABLE 1. EFFECTS OF HYPEROXIA ON SURFACTANT PROTEIN AND mRNA LEVELS

Animal species	*O_2 exposure*	*SP levels (lavage)*	*SP mRNA levels (tissue)*	*Reference*
Rat	85%, 7 days	SP-A ↑ SP-B ↑ SP-C ↑	SP-A ↑ SP-B ↑ SP-C ↑	34, 35
Rabbit	100%, 64 h		SP-A ↑ SP-B ↑	25
Baboon (preterm)	100%, 6 days		SP-B ↑ SP-C ↑	32
Hamster	100%, 8 days		SP-A ↓ SP-B ↓ SP-C ↓	33
Mouse	95%, 3–5 days		SP-B ↑	43
Lamb (preterm)	100%, 10 h		SP-A ↑ SP-B ↑	44
Rat	95%, 36–60 h		SP-A ↑ SP-B ↑ SP-C ↑	7
Rat	95%, 12 h 95%, 60 h		SP-D ↑ SP-D ↓	5
Rabbit (newborn)	95%, 4 days		SP-A ↑	18
Baboon (preterm)	100%, 10 days	SP-A ↑ SP-D ↑	SP-A ↑ SP-D ↑	10
Rat (newborn)	100%, 6 h		SP-A ↑ SP-B ↑ SP-C ↑	39
Rat (newborn) (nitrofen-CDH*)	100%, 6 h		SP-A ↓ SP-B ↓ SP-D ↓	39
Rat (newborn)	100%, 8 days		SP-A ↑ SP-B ↑ SP-C ↑ SP-D ↑	42

*CDH, congenital diaphragmatic hernia; ↑, increase; ↓, decrease.

In adult B6C3F1 and FVB/N mice, hyperoxia had distinct cell type-specific effects on the expression of SP-B in the lung. In contrast to its inductive effects on SP-B expression in bronchiolar and alveolar type II cells in rats and rabbits, hyperoxia selectively increased the expression of SP-B and its mRNA in bronchiolar but not in alveolar type II cells of adult mice (43). Increased expression of SP-B mRNA in bronchiolar epithelium was associated with increased staining for SP-B proprotein. In a study of time-course effects of 95% O_2 on the expression of surfactant protein genes in adult rats, it was found that the expression of SP-A, SP-B, and SP-C mRNAs were transiently decreased after 12 h of exposure, but increased after 36 and 60 h of exposure (7). The effects of hyperoxia to increase whole-lung surfactant protein mRNAs was paralleled by similar effects on their expression in alveolar type II and Clara cells (7). Exposure of adult rats to 95% O_2 significantly increased SP-D mRNA levels after 12 h of exposure, but decreased its levels with continued exposure for 60 h (5). The increases in SP-D mRNA levels were associated with increased numbers of alveolar type II cells and bronchiolar epithelial cells expressing SP-D mRNA and increased expression of mRNA in the two cell types (5). Paradoxically, increased SP-D mRNA was associated with decreased levels of SP-D protein as assessed by western blotting (5). The decrease in SP-D levels appeared to be restricted to alveolar type II but not bronchiolar epithelial cells (5). Hyperoxia also had distinct effects on the regulation of surfactant protein gene expression in adult hamsters (33). In adult hamsters exposed to 100% O_2 for up to 8 days, SP-A expression increased at earlier time periods of exposure, but decreased significantly by day 8. SP-B expression decreased continuously and SP-C expression, although unchanged at early time periods, decreased subsequently (33).

Regulation in newborn animals

Interestingly, in the nitrofen-induced congenital diaphragmatic hernia model of newborn rats, hyperoxia did not increase SP-A and SP-D mRNA levels, although it increased SP-A and SP-D mRNA levels in control animals after 6 h of exposure (39). SP-B and SP-C mRNA levels did not change in control or nitrofen-induced diaphragmatic hernia rats exposed to hyperoxia (39). This indicates that the hypoplastic lung in nitrofen-induced diaphragmatic hernia is not responsive to the effects of oxygen to modulate surfactant protein gene expression. In a neonatal model of hyperoxia-induced fibrosis, newborn rabbits exposed to 95% O_2 showed increased expression of SP-A mRNA after 4 days of exposure, however, SP-B and SP-C mRNA expression did not change (18). In newborn animals that had survived exposure to 95% O_2, continued exposure to 60% O_2 did not change whole-lung SP-A, SP-B, and SP-C

mRNAs, but *in situ* hybridization analysis revealed that in areas marked by inflammation SP-A, SP-B, and SP-C mRNA expression was markedly increased (18). In newborn rats (2 days of age) exposed to 100% O_2 for up to 8 days, SP-A, SP-B, SP-C, and SP-D mRNA levels were elevated (42). The pattern of increase of each mRNA was different. Whereas SP-A and SP-B mRNA levels progressively increased during exposure, SP-C and SP-D mRNAs levels increased after 1 day of exposure and remained elevated during the course of exposure (42). The increases in SP-A and SP-D mRNA levels were associated with similar changes in their levels in lung lavage (42). Interestingly, hyperoxia-induced expression of surfactant protein mRNAs was associated with the increased expression of thyroid transcription factor-1 (TTF-1/Nkx2.1) (42), a key transcription factor that controls the expression of surfactant protein genes.

Regulation in premature animals

In 140-day gestational age premature baboons maintained on ventilatory support, exposure to 100% O_2 for up to 10 days did not alter SP-A mRNA levels, but increased SP-B and SP-C mRNA levels after 6 days of exposure (32). After 10 days of exposure, there were no significant increases in the levels of SP-B and SP-C mRNAs (32). In preterm lambs, hyperoxic regulation of surfactant protein gene expression was dependent on the gestational age (44). Whereas hyperoxic exposure had no effect on SP-A, SP-B, and SP-C mRNA levels in gestational age 120-day lambs, it selectively increased SP-A mRNA levels in 132-day lambs and increased both SP-A and SP-B mRNA levels in 139-day lambs (44). Hyperoxia did not alter SP-C mRNA levels in preterm lambs at 120, 132, and 139 days of gestation (44). In preterm baboons ventilated with 100% O_2 for 10 days, increased tissue expression of SP-A and SP-D mRNAs was found; however, increased expression of SP-A and SP-D mRNAs was not associated with similar increases in the lavage, suggesting regulation at translational and secretion levels (10).

OXYGEN REGULATION OF SURFACTANT PROTEIN GENE EXPRESSION IN FETAL LUNG *IN VITRO*

Oxygen exerts dose-dependent stimulatory effects on SP-A mRNA levels in midgestational age human fetal lung tissues *in vitro* (3). The positive effects of oxygen were clearly seen for SP-A and SP-C mRNAs with insignificant effects on SP-B mRNA levels (3). Choline incorporation into total phosphatidylcholine and DPPC was also increased in oxygen treated fetal lung explants, indicating positive effects on surfactant phospholipid synthesis (3). Oxygen-dependent increase in SP-A mRNA levels was found to be due to both an increase in transcription rate and mRNA stability (4). Oxygen was also found to modulate the differentiation of human fetal lung *in vitro* and its responsiveness to cyclic AMP (2). Maintenance of midgestational age human fetal lung tissues in vitro in 1% O_2 blocked the morphological differentiation of tissue and SP-A gene expression (2). Transfer of tissues maintained in 1% O_2 to an environment of 20% O_2 promoted rapid morphological differentiation of the tissue and induction of SP-A gene expression (2). These data indicate that oxygen plays a permissive role in promoting the morphological and biochemical differentiation of fetal lung tissue. A role for oxygen in the differentiation of fetal lung is further suggested by the observations that fetal lung at midgestation is poorly vascularized, having an oxygen concentration in the range of 1–2%. With increasing gestation, the growth and infiltration of capillaries into regions surrounding ductular structures cause increased blood flow, resulting in enhanced oxygen levels and associated differentiation of fetal lung.

CONCLUDING REMARKS

Molecular mechanisms underlying hyperoxia regulation of surfactant protein gene expression are not understood. Studies in human fetal lung *in vitro* have indicated that both transcriptional and mRNA stability mechanisms contribute to oxygen increase of SP-A gene expression (4). Whether similar mechanisms mediate surfactant protein gene regulation in animals is not known. It has been hypothesized that the inner mitochondrial membrane is a site where oxygen radicals are excessively produced in hyperoxia (38). Whether hyperoxia acts directly on surfactant protein genes to regulate their expression or modulates other factors to exert secondary effects is not clear.

Cellular effects of reactive oxygen species are partly the result of direct oxidation of cellular components. Alterations in the cellular redox status due to oxidative stress may modulate gene expression via activation of distinct signaling pathways. Increasing the cellular ratio of glutathione disulfide (GSSG) to reduced glutathione (GSH) by use of pharmacological agents decreased SP-A and SP-B mRNA levels in H441 cells, a human cell line with characteristics of bronchiolar (Clara) epithelial cells (28). *N*-Acetylcysteine reversal of SP-A and SP-B mRNA inhibition was associated with decreased ratios of cellular GSSG/GSH (28). These data suggest that cellular glutathione redox status influences surfactant protein gene regulation. A role for cellular glutathione redox status in the control of surfactant protein gene expression in hyperoxia is further suggested by the finding of increased levels of GSH in the bronchoalveolar lavage fluid of rats exposed to 80% O_2 for 5 days (27). Because hyperoxia increases surfactant protein gene expression, these data strongly suggest a link between increased ratio of GSH/GSSG and up-regulation of surfactant protein gene expression. Signal transduction pathways and molecular mechanisms that mediate redox regulation of surfactant protein gene expression are not known.

Surfactant protein promoter activity is dependent on the interactions of a number of transcription factors that bind to cognate DNA elements on the promoter (Fig. 1) (12). Combinatorial and stereospecific interactions between the transcription factors and the promoter are necessary for promoter activity (6). TTF-1/Nkx2.1 (8), specificity protein 1 (Sp1)(45), activator protein-1 (AP-1) (1), and nuclear factor-κB (37) are some of the redox-sensitive transcription factors that have been shown to be important for surfactant protein promoter activity (12). As such, these and other transcription factors yet to be identified may serve as mediators of oxidant stress to control surfactant protein gene regulation. Whether hyperoxia alters the DNA binding activities and/or expression lev-

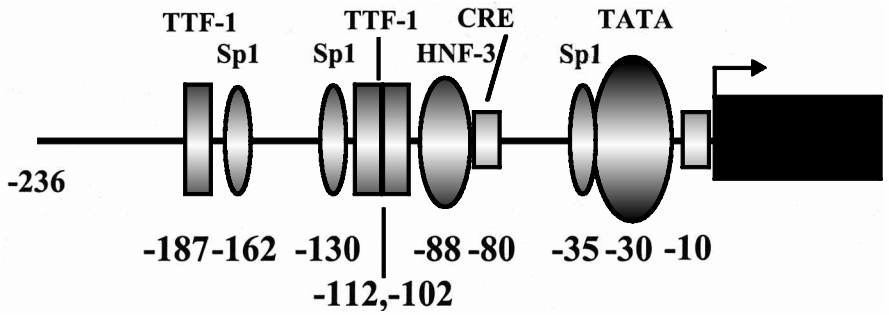

FIG. 1. Schematic diagram of the minimal promoter region of rabbit SP-B gene. The locations (in base pairs) of functionally important cis-DNA elements and the TATA sequence relative to the start site of transcription (arrow) are shown. The DNA binding sequence and the location of the cis-DNA elements are very similar in the minimal promoter regions of human and mouse SP-B genes. Publications dealing with the identification of SP-B cis-DNA elements are reviewed in reference 12. CRE, cyclic AMP regulatory element; HNF-3, hepatocyte nuclear factor 3.

els of redox-sensitive and other transcription factors to modulate surfactant protein promoter function is not known. Because hyperoxia increases surfactant protein gene expression, it is unlikely that direct oxidation of transcription factors leads to such an increase as oxidation results in the reduction of DNA binding activities of TTF-1/Nkx2.1 (8), Sp1 (45), and AP-1 (1) transcription factors. Therefore, it seems unlikely that up-regulation of surfactant protein gene expression in hyperoxia is the direct result of modification of transcription factors by oxidation, but may be due to alterations in the DNA binding activity and/or expression levels of transcription factors. Increased expression of TTF-1/Nkx2.1 in hyperoxia (42) could be one such mechanism for up-regulation of surfactant protein gene expression.

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ABBREVIATIONS

AP-1, activator protein-1; DPPC, dipalmitoylphosphatidylcholine; GSH, glutathione; GSSG, glutathione disulfide; Sp1, specificity protein 1; SP-A, SP-B, SP-C, and SP-D, surfactant protein A, B, C, and D, respectively; TTF-1/Nkx2.1, thyroid transcription factor 1.

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