Surfactant

Article

Une nouvelle génération de surfactants de synthèse

Exogenous surfactant therapy: new synthetic surfactants

Th. Lacaze-Masmonteil

Department of Pediatrics, Stollery Children's Hospital, Women and Children's Health Research Institute, Edmonton, Alberta, Canada

Summary

There are numerous pulmonary conditions in which qualitative or quantitative anomalies of the surfactant system have been demonstrated. In premature newborns with immature lungs, a functional deficit in surfactant is the main physiopathologic mechanism of the neonatal respiratory distress syndrome (RDS). Since the landmark pilot study of Fujiwara, published more than 20 years ago, the efficacy of exogenous surfactant for the treatment of neonatal RDS has been established by numerous controlled studies and meta-analyses. Enlightened by a growing insight into both the structure and function of the different surfactant components, a new generation of synthetic surfactants has been developed. Various complementary approaches have confirmed the fundamental role of the two hydrophobic proteins, SP-B and SP-C, in the surfactant system, thus opening the way to the design of analogues, either by chemical synthesis or expression in a prokaryotic system. An example of these peptide-containing synthetic surfactant preparations, lucinactant (Surfaxin®), has been recently tested in comparison to a synthetic surfactant that does not contain protein as well as to animal derived surfactant preparations. Major clinical outcomes between lucinactant and animal-derived surfactant preparations were fund similar in two randomized controlled trials, opening the way to a new generation of synthetic surfactants in the near future.

Résumé

Le développement et la mise sur le marché de surfactants d'origine bovine ou porcine, comprenant un mélange de phospholipides et protéines hydrophobes spécifiques SP-B et SP-C, ont révolutionné le traitement de la maladie des membranes hyalines du grand prématuré. Une nouvelle génération de surfactants synthétiques, constituée de phospholipides et d'analogues peptidiques des protéines spécifiques, a récemment émergé. Lucinactant (Surfaxin®), un surfactant de synthèse constitué par l'addition d'un analogue de la protéine SP-B à des phospholipides, a été évalué par des essais cliniques contrôlés avec des résultats prometteurs. L'impact de l'émergence de cette nouvelle classe de surfactants est potentiellement majeur. Ces surfactants disponibles en quantité illimitée et à moindre coût ont le potentiel de profondément modifier la prise en charge de la maladie des membranes hyalines dans les 10 prochaines années.

Mots clés : Surfactant, Prématurité, Maladie des membranes hyalines

* Auteur correspondant.
e-mail : thierrylacaze@cha.ab.ca

Pulmonary surfactant, a multicomponent complex of several phospholipids, neutral lipids and specific proteins, is synthesised and secreted into alveolar spaces by type II epithelial cells [1,2]. The main functions of pulmonary surfactant are reducing the collapsing force in the alveolus, conferring mechanical stability to the alveoli, and maintaining the alveolar surface relatively free of liquid [3]. Administration of a natural animal-derived surfactant to a surfactant-deficient preterm animal or human newborn decreases the minimum pressure required to open the lung, increases the maximal lung volume, and prevents lung collapse at low pressure [4]. Phospholipids are primarily responsible for the surface-tension lowering activity of surfactant, but other components present in animal-derived surfactants also play important roles.

1. Pulmonary surfactant: structure and function

Surfactant is primarily composed of phospholipids and proteins. Most of the phospholipids consist of phosphatidylcholine (PC), and one particular PC molecule, DPPC (dipalmitoyl phosphatidylcholine), is the most prevalent component [5]. The structure of DPPC is suited to form a stable monolayer generating the low surface tension required to prevent alveolar collapse at end-expiration. Phosphatidylglycerol (PG) also contributes to monolayer formation; its synthesis is restricted to type II alveolar cells, and its detection in amniotic fluid is a reliable predictor of lung maturation [6]. Phospholipids alone are far from exhibiting all the biophysical properties of pulmonary surfactant. These properties include the ability to generate low minimum surface tension on dynamic compression, to rapidly absorb from the subphase to the interface, to respread when collapse occurs after condensation, and to vary surface tension during expansion and compression at each respiratory cycle. In this respect, the contribution of low molecular weight SP-B and SP-C proteins to both structural organization and functional durability is essential [7,8].

Through its life cycle, the surfactant material undergoes a series of important structural and functional transitions [9,10]. The first, lamellar bodies, the intracellular storage form of surfactant, appear within the distal epithelial cells at around 22 weeks' gestation. They become numerous and enriched with a functional surface-active material only in the last weeks of a normal pregnancy. At birth, numerous lamellar bodies are actively secreted by exocytosis. In the hypophase, the thin fluid layer covering the alveolar epithelium, lamellar bodies unpack and generate tubular myelin, a transitional highly ordered lattice-like structure representing the extracellular pool of surface-active material from which the monolayer is formed. During each respiratory cycle, pauci or unilamellar small vesicles with low surface-active properties are generated from the monolayer and the tubular myelin. They represent a catabolic form destined for clearance. After birth, an efficient recycling of the alveolar surfactant pool is initiated. In term newborn rabbits, more than 90% of the alveolar phosphatidylcholine (PC) is recycled, processed by type II alveolar cell, incorporated into lamellar bodies, and eventually secreted. Tightly associated with phospholipids, the hydrophobic proteins SP-B and SP-C have an essential role in enhancing the biophysical activity of phospholipids [8,11]. These proteins promote the rapid absorption of phospholipids at the air-liquid interface and account for the sustained low surface-tension activity after dynamic compression.

SP-B, a 79 amino-acid peptide, has the most important surface-active permissive effect upon phospholipids [12]. Lethal respiratory failure occurs at birth in homozygous mice harbouring an SP-B gene inactivated after homologous recombination [13]. The SP-C precursor is not correctly processed, and neither lamellar bodies, nor tubular myelin are detectable in type II cell cytoplasm and extracellular alveolar spaces, respectively. These features confirm the essential role of SP-B in surfactant metabolism. SP-B deficiency, inherited as an autosomal recessive condition, has been identified in full-term newborn infants exhibiting severe and fulminant respiratory failure [14]. Although the frame-shift insertion of two nucleotides at the codon 121 is the most frequently encountered mutation (121ins2), genetic analysis of affected infants has identified more than 20 other mutations, most of them severely affecting composition, structure and function of surfactant [15,16].

SP-C, a 35 amino-acid peptide, is made of a very large proportion of hydrophobic residues [8,11,17]. Its hydrophobic character is strengthened by two palmitoyl residues covalently linked to cysteine residues. Like SP-B, SP-C dramatically enhances the spreading of phospholipids. Whereas SP-C knocked-out animals do not manifest any respiratory symptoms at birth, SP-C-deficient adult animals develop pneumonitis and emphysema [18]. The recent characterisation of a dominantly inherited mutation in the SP-C gene of siblings with interstitial lung disease suggests that either inadequate SP-C synthesis or the accumulation of an abnormal SP-C precursor may account for some forms of chronic interstitial lung disease in childhood [19,20].

2. The different exogenous surfactants

Exogenous surfactants are currently classified into two families [21-23]. The mammalian surfactant preparations (animal