Role of surfactant in Eustachian tube physiology: a review

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Role of surfactant in Eustachian tube physiology: a review

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Background: Surfactant has been demonstrated biochemically and morphologically in the Eustachian tube. Exogenous surfactant administration in animal models of otitis media with effusion has shown beneficial effects. An up-to-date review of the role of surfactant in Eustachian tube physiology is warranted.

Materials and Methods: A search of the English language literature using PubMed, Medline and Ovid databases, as well as the Google search engine was conducted, under the headings (surfactant) and (Eustachian tube). Relevant articles were analysed.

Results: Surfactant lipids and proteins play an important role in the mucociliary clearance, mucosal immunity and mechanical properties of the Eustachian tube.

Conclusion: Application of exogenous surfactant in cases of otitis media with effusion represents a novel non-surgical modality to induce resolution of this condition. Studies in humans are awaited.

Keywords: Surfactant, Eustachian tube, Middle ear.

INTRODUCTION

Following the discovery of pulmonary surfactant and its role in neonatal respiratory distress syndrome, surface-tension-lowering substances have been detected in the Eustachian tube (ET).1,2

Hypotheses have been developed regarding the role of ET surfactant abnormalities in the development and maintenance of otitis media with effusion (OME).3,4

Experimental studies on the efficacy of surfactant administration in the resolution of OME in animal models are ongoing, with hopes for human application.5-11

The term (surfactant) is an abbreviation for (surface-active agent). Surfactant molecules have two distinct regions in their chemical structure; one is hydrophilic (polar), and the other is hydrophobic (non-polar). These molecules are referred to as amphipathic. Surfactants tend to adsorb at interfaces, with the hydrophobic group protruding into the air and the polar group acting as an anchor in the biological surface. The reason for the reduction in surface tension imparted by the surfactant molecules is that the forces of attraction between surfactant and water molecules are less than those between two water molecules; hence, the contraction force is reduced.12 The major component of biological surfactants is phospholipids, which are amphipathic molecules. In addition, natural surfactants contain proteins, which are essential for surfactant homeostasis and physical architecture.13
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In this article, the biological role of surfactant, in relation to ET physiology, is explored. A search of the literature using PubMed, Medline and Ovid databases as well as the Google search engine, was conducted. The keywords were (surfactant) and (Eustachian tube). Relevant articles in the English language literature from 1970 till 2011 were studied.

Physicochemical properties of ET surfactant

The major components of ET surfactant are phospholipids and surfactant-associated proteins. Phospholipids are esters of fatty acids with alcohols, which contain a phosphoric acid residue. They frequently have nitrogen-containing bases such as choline and ethanolamine. The most important neutral lipid in surfactants is the steroid, cholesterol. The phospholipid profile of porcine ET lavage fluid has been analysed by Paananen et al, and compared with that of bronchoalveolar lavage fluid.

The most important difference was that dipalmitoylphosphatidylcholine, the major surface-active component of pulmonary surfactant, had a low concentration in ET lavage fluid. The phospholipid profile of ET lavage fluid suggested that ET surfactant had detergent-like properties. In contrast to the surfactant role in the lung, where gas delivery is tidal, the detergent-like properties of ET surfactant may be more important in the ET, where gas exchange is accomplished only intermittently.

Surfactant-associated proteins identified in the alveolar lining of the lung include surfactant proteins (SPs), SP-A, SP-B, SP-C, SP-D. SP-A and SP-D have been identified in porcine ET lavage fluid, and have been immunolocalised near the mucosal folds in the floor part of the ET. SP-A and SP-D are hydrophilic glycoproteins, which belong to the family of C-type lectins (known as collectins). They are important molecules in the innate immune system against microorganisms. In addition, SP-A enhances the surface-activity of phospholipids and it maintains the homeostasis between the extra- and intracellular surfactant pools. SP-B has been identified in porcine ET lavage fluid and was found to be expressed in the ET epithelium. SP-B is a hydrophobic protein which increases the surface adsorption and decreases the surface tension of surfactant phospholipids. SP-A, SP-B and SP-D have been identified in human ET lavage fluid by Western blotting.

Another recently identified surfactant-associated protein, PLUNC (Palate, lung, nasal epithelium clone) is expressed in the mucosa of the human respiratory tract. This protein had the physical properties of a surfactant in the ET function of maintaining a normal middle-ear pressure. Moreover, it is essential for periciliary fluid homeostasis, and it functions as an innate immunity molecule. PLUNC is a hydrophobic protein capable of binding lipids and it probably plays a significant role in ET physiology.

Surfactant and the mucociliary clearance of the ET

The mucociliary clearance in the ET is directed from the middle ear to the nasopharynx, and is essential for maintaining the sterility of the middle-ear cavity. The surfactant layer reduces surface tension at the mucus-air interface and promotes particle displacement into the mucus layer. Surfactant has been shown to maintain the ciliary beat frequency in guinea pig trachea. Moreover, the enhancing effect of surfactant on ciliary beat frequency was dose dependent. Recently, the surfactant associated protein, PLUNC, was found to be a volume sensor, which is essential for periciliary fluid homeostasis, and hence for optimum coupling of the cilia with the gel layer.

The rheological properties of mucus in the mucociliary blanket are determined by the quantity and character of mucins. Mucins are a family of glycoproteins which have strong adhesive properties, owing to intermolecular noncovalent interaction between various sugars on neighboring glycan chains. Differences in mucin gene polymorphisms have been found in OME patients, compared to controls. Exogenous phospholipid surfactants have been found to reduce the viscoelastic properties of mucus, increase its hydration and enhance mucociliary transportability. It has been hypothesized that surfactant acts as a lubricant, facilitating the sliding of the mucus gel layer on the periciliary fluid. The physiological function of natural surfactant requires the interaction of SP-A and SP-B, as well as calcium ions with the phospholipids to form the ordered, three-dimensional, architecture of the surfactant layer.

Otitis media with effusion (OME) is frequently associated with a mucus plug in the ET lumen. As proposed by Sadé, propagation of this plug towards the nasopharynx contributes to the negative middle-ear pressure observed in ears with OME. An interesting field, that has been evolving over the last decade, is the study of fluid transport at a microscopic scale, microfluidics, in biological systems. Tavana and colleagues have recently devised a microengineered channel composed of respiratory epithelial cells. Propagation of liquid plugs through this channel caused significant damage to the cells, corresponding to the number of events of plug actuation. They postulated that the natural surfactant, present on the epithelial lining, protects the underlying cells from irreversible damage caused by plug propagation. An experimental study on guinea pigs, using scanning electron microscopy, showed that surfactant protects ET mucosal cilia and minimizes goblet cell hyperplasia in an OME model.
Surfactant and mucosal immunity of the ET

The middle-ear cavity is normally sterile. Bacterial colonization in the nasopharynx starts soon after birth. Potential middle-ear pathogens may cause otitis media by retrograde migration along the ET. Nasal or postnasal obstruction from viral infections, allergies or adenoid hypertrophy may lead to insufflation of nasopharyngeal secretions into the ET during swallowing. The mucociliary blanket and the molecules of innate immunity in the tubal mucosa are the first-line defense against microbes entering the ET.

It has been found, in mice, that the transitional epithelium in the dorsal part of the ET produces surfactant. It has been hypothesized that the dorsal part of the ET is involved primarily in the ventilatory function associated with tubal opening. Recent studies have shown that the surfactant film is maintained during changes of the luminal surface area, such as during opening and closure of the tubal lumen. This homeostasis of the surfactant film is attributed to the composition of lipids, as well as to the crucial presence of SP-B. Hills used a special fixative for electron microscopy that does not destroy lipids, and allows visualization of lipid structure. He used this method for studying the human ET surfactant, and he documented the presence of an oligolamellar lining of surfactant over the epithelial surface. This oligolamellar lining was strongly coherent and also spanned the cellular junctions. An experimental study showed that surfactant promotes the displacement of particles from air to the mucosal lining by the lowering of the surface tension of the surface-active film. Most particles of a size less than 10 microns, including bacteria and viruses, would behave similarly. These particles would be pulled towards the epithelium by surface forces imparted by the surfactant, where they come into contact with macrophages and cilia.

Surfactant proteins (SPs), SP-A and SP-D have been detected in human and animal ETs. Of evolutionary significance, SP-A is found in the lungs of lungfish, which are considered the direct ancestors of terrestrial animals.

SP-A and SP-D are glycoproteins, belonging to the collectin family of proteins. They contain a collagen-like region and a C-type lectin domain. The carbohydrate-recognition (lectin) domain mediates the selective recognition of pathogenic organisms and the binding to several soluble and membrane-associated ligands, which are not usually found in mammalian cells. SP-A and SP-D bind bacteria and viruses with high affinity due, on one hand, to the high carbohydrate ligands on the microbial surface, and on the other hand, to the degree of oligomerization of the collectin. They function as opsonins and can enhance the killing of microorganisms by phagocytosis. In addition, SP-A and SP-D have immunomodulatory functions in regulating proinflammatory cytokine and free radical production by phagocytes; thereby checking the inflammatory response. The immunomodularity function of SP-A is suggested by an increased SP-A immunoactivity in rheumatoid disease. Elevated free radical levels are an important pathological feature in otitis media with effusion, both in humans and in animal models. Genotyping of the SP-A gene locus has shown that children with recurrent acute otitis media had different haplotypes and genotypes, compared with those in the control population. In addition to the roles of SP-A and SP-D in immunity, the surfactant associated protein PLUNC was found to have anti-microbial properties in the ET.

Surfactant and the mechanical properties of the ET

There is roughly an 8 to 12-mm segment in the middle of the cartilaginous ET that is closed at rest, with mucosal surfaces in apposition, and therefore functioning as a valve. This closed segment allows for protection of the middle ear from nasopharyngeal secretions. In the closed middle-ear cleft, the pressure gradients of various gases across the mucosal lining determine the middle-ear pressure. Diffusion of gases between the middle-ear cleft and the mucosal blood capillaries is determined by the relative partial pressures of each gas in the middle-ear space and the blood. The mastoid air cells act as a buffer in middle-ear pressure regulation. The ET lumen opens from the closed position, during swallowing, for about 0.4 seconds. This brief opening allows for equilibration of pressure between the middle-ear space and the atmosphere, thereby ensuring optimum acoustic functions of the tympanic membrane and the middle ear.

It has been demonstrated, in experimental animals, that modulation of the luminal surface condition of the ET could have effects on the mechanical properties of the ET. In otologically healthy ears, surfactant applied into the middle ear, or administered intranasally, reduced the passive opening pressure of the ET. The authors in these studies attributed this surfactant effect to the lowering of surface tension at the mucosal lining of the tubal lumen, according to La Place law. The law of La Place states that, for a given tube radius, the higher the surface tension inside the tube, the greater is the transluminal pressure required to maintain patency of the tube. However, Hills argued that this mechanical effect of surfactant was due to the action of surfactant as a release agent (antistick or antiadhesive behaviour), which opposes the strongly adhesive nature of proteins in apposed surfaces. In favour of Hills' argument is that the phospholipids in ET lavage fluid are not strongly surface active, as they are in bronchoalveolar lavage fluid.
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Paananen and colleagues proposed that the phospholipid profile in porcine ET lavage fluid had detergent-like properties.\textsuperscript{15} These properties are more relevant in the ET function of facilitating tubal opening during swallowing, in contrast to the high surface activity of pulmonary surfactant required for the tidal gas delivery. Moreover, comparative studies on pulmonary surfactant in non-mammalian vertebrates suggest that specific lipid profiles contribute to the action of pulmonary surfactant as a release agent, which is more relevant to the physiological demands in these species.\textsuperscript{70} The role of surfactant in facilitating tubal opening is very important in reducing physical stresses which could peel apart the mucosal epithelial cells.\textsuperscript{71,72}

Another parameter in ET mechanics that had been studied is the ET closing pressure.\textsuperscript{73} ET closing pressure is related to the extraluminal forces imparted by the elasticity of the tubal cartilage and the static pressure exerted by soft tissue around the tube.\textsuperscript{74,75}

The difference between the ET opening pressure and closing pressure is thought to reflect luminal forces, such as adhesion across the tubal walls. Exogenous surfactant was found to reduce this difference, compared to placebo.\textsuperscript{73} Further parameters studied in ET mechanics were compliance and hysteresis of the ET.\textsuperscript{76} Low compliance reflects a rigid or inelastic ET that is difficult to open. Conversely, high compliance reflects what is commonly known as a (floppy) tube, which may impair the tubal protective function. Removal of the mucous blanket led to a decrease in compliance, and after instillation of surfactant, the compliance returned to baseline values. Hysteresis occurs when the forces acting on the ET are dissipated, such that they do not produce the same cross-sectional area during inflation and deflation. Hysteresis was reduced after washing out of the ET mucous layer, but returned to baseline values on surfactant administration.\textsuperscript{70} These results concluded that a normal surfactant layer in the ET is beneficial for ET mechanics.

Dysfunction of the mechanical properties, affecting the opening of the ET, is recognized as an important factor responsible for the development and maintenance of otitis media with effusion (OME).\textsuperscript{77} ET dysfunction is proposed to cause negative middle-ear pressure, according to the (hydrops ex vacuo) theory. According to this theory, the middle ear is maintained at a relative positive pressure with respect to the summed partial pressures of gases in the blood and tissue. In the absence of effective ET dilations, the pressure gradients result in a diffusive gas flux from middle ear to tissue, resulting in a negative middle-ear pressure.\textsuperscript{59} Tympanic membrane retraction is a common observation in OME.\textsuperscript{78} OME is commonly treated surgically by insertion of ventilation tubes alone, or in combination with adenoidectomy.\textsuperscript{79}

Given the physiological role of surfactant in ET function, the therapeutic administration of surfactant in cases of OME represents a novel modality to induce resolution of this condition.\textsuperscript{80} Studies in experimental animal models of OME have shown that nasal administration of surfactant resulted in normalization of the otoscopic findings, improvement in the mechanical properties of the ET, as well as the induction of histological resolution of the inflammatory changes in the middle ear.\textsuperscript{5-10} Recently, Jang and colleagues used laser Doppler vibrometry to study tympanic membrane vibration in ears with experimentally induced OME. Laser Doppler vibrometry has a much greater sensitivity in the assessment of tympanic membrane vibration amplitude and velocity, compared to tympanometry. The authors noted the recovery of tympanic membrane vibration in the animals treated with intranasal aerosolized surfactant.\textsuperscript{11} The results of the previous experiments suggested that nebulized surfactant or surfactant administered by a metered dose inhaler could be a clinical practice for non-surgical treatment of OME in future. However, further studies are required before human application.

CONCLUSION

The physiological roles of surfactant in the Eustachian tube include normal functioning of the mucociliary blanket and an important innate defense mechanism against microbes. Its role in the mechanical properties in the Eustachian tube offers potential therapeutic implications in the management of otitis media with effusion.

REFERENCES


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