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Particles on the lung surface - physicochemical and hydrodynamic effects

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ABSTRACT

The paper highlights and discusses the role of interfacial phenomena in the interactions between inhaled solid particles with different properties (size, structure, surface characteristics) and air/liquid interface of the alveolar region of the lungs. The greatest attention is paid to man-made nanosized and nanostructured particles which often belong to the class of "engineered particles". Their applications in several novel technologies may be associated with accidental particle release to the air and formation of potentially harmful aerosol. Extraordinary, dynamic surface-active properties of the lung surfactant, which are responsible for several physiological functions - including the pulmonary mass transfer - may be altered by such inhaled particles in a material- and dose-dependent manner. Certain effects can be assessed by specialized experimental in vitro methods allowing predictions of possible in vivo interactions. On the other hand, interactions with the lung surfactant can modify the original properties of inhaled particles which in turn will influence their bioavailability or toxicity. All mentioned effects are dependent on particles properties as proven by numerous studies, however such results should be carefully judged due to essential differences in experimental methodology used. The paper also discusses some ideas related to the practical meaning of discussed effects for novel concepts of pulmonary drug delivery by inhalation.

1. Introduction

Sophisticated structure of the respiratory system assures the effective gas exchange during breathing. After distribution via the system of branching tubes which form the bronchial tree, inhaled air finally arrives to the alveoli - the final respiratory structures where oxygen and carbon dioxide permeate to/from the blood. The pulmonary zone has the effective surface area about 100 m^2 and it is lined with very thin layer of aqueous fluid. This pulmonary liquid contains a mixture of surface-active components known as the lung surfactant (LS). LS is composed of lipids and proteins secreted by alveolar type II cells, and these compounds are capable of reducing dynamically the surface tension of pulmonary liquid during breathing cycle. This property obviously influences the mechanical characteristics of lungs, since low surface tension (γ) at the beginning of the inspiration phase, i.e. at high surface compression, makes inspiration easier [1••]. It is recognized that surfactant deficiency or inefficiency are the reasons of life-threatening pulmonary dysfunction known as the Respiratory Distress Syndrome [2]. It is important to stress that many physiological functions of LS are strictly related to its surface-active properties revealed under dynamic conditions of breathing. From practical point of view, the dynamics of this system is the of most importance since the equilibrium properties do not reflect the physical state of a living organism.

LS is also the primary barrier of contact between the pulmonary part of the respiratory system and inhaled foreign substances. These additional components of air may come from natural or anthropogenic sources and can be in form of a gas or aerosol. Many of them are inhaled accidentally being air contaminants but some are intentionally delivered to the lungs (e.g. cigarette smoke, e-cigarette vapor, inhaled aerosol medicines; [3•]). Aerosols may be composed either solid particles or liquid droplets will spread along the air-liquid interface after deposition. Chemicals delivered to the lungs can directly influence the LS activity if they are surface-active or chemically reactive towards LS components. Solid particles which land on the surface of pulmonary alveoli may be either soluble or insoluble in the pulmonary liquid, however, at the initial contact they directly interact with the air-liquid interface (ALI).

2. Particle inhalation and deposition in the lungs

Deposition of inhaled aerosol particles inside the respiratory system depends on several factors. Particle size, shape and density together with the mode of breathing and health status (e.g. degree of airways obturation) determine the depth of aerosol penetration and the efficiency of deposition due to different physical mechanisms (sedimentation, impaction, direct interception, Brownian diffusion) in each part of the respiratory system (upper airways, bronchial tree, gas-exchange area) [4•]. It has been recognized that only particles smaller than approximately 5 μm can penetrate to the peripheral airways during inhalation, which means that only such particles can reach the LS-abundant alveolar region of the respiratory system. Nevertheless, not all such particles

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are deposited efficiently in the lungs; for instance, particles within the size range of 200–800 nm are mostly exhaled. This effect has found a practical application in e-cigarettes, which have been designed in a way to produce aerosol that can be exhaled as a dense cloud in order to resemble visually the exhaled smoke of conventional cigarettes [5].

In general, inhaled nanoparticles (NPs) and particles with size of a few micrometer (also those composed of aggregated NPs, i.e. nanostructured particles: NSPs) can land in pulmonary alveoli which are covered by a thin layer of aqueous layer. As soon as a particle touches the liquid, it generates a series of physicochemical events which are initially started by a direct interaction with the ALI, characterized by the extraordinary properties described in the following section.

3. Lung surfactant characteristics and biophysical properties

3.1. Lung surfactant composition

Lung surfactant (LS) is a mixture of biosurfactants naturally present in the aqueous layer which lines the surface of the alveolar region of the respiratory system. Lung surfactant of human and other mammals is composed of: phospholipids (PLs - approximately 80% by mass), neutral lipids (mainly cholesterol - 5–10%), and surfactant proteins (hydrophilic: SP-A and SP-D, hydrophobic: SP-B and SP-C - approximately 10%) Surfactant PLs contain ca. 80% phosphatidylcholines (PCs), ca. 12% phosphatidylglycerol (PG), and smaller amounts of phosphatidylinositol (PI), phosphatidylethanolamine (PE), lysobis-phosphatidic acid, and sphingomyelin [6]. The major PC is dipalmitoylphosphatidylcholine (DPPC: 30–50%), while the most important PG is dipalmitoylphospahatidylglycerol (DPPG: ca. 10%). As stated earlier, the presence of such compounds in the lungs assures several vital respiratory functions. One of this functions is related to the pulmonary mass transfer.

3.2. Marangoni flows on the alveolar surface

Motion of a thin liquid layer propelled by surface tension gradients, $\nabla\gamma$, and their significance for convective mass transfer in the lungs was postulated by Gradoń and Podgórski [7•] and Podgórski and Gradoń [8]. These authors demonstrated theoretically that periodic variations of surface tension in the LS system caused by surface area changes during breathing cycle, can produce the Marangoni flows. The oscillatory motion of alveolar liquid is not fully symmetric even in idealized spherical geometry since the pattern of surface tension changes during surface pulsation is not identical. These alveolar Marangoni flows are capable of pushing out particles deposited on the pulmonary surface – such effect forms the hydrodynamic mechanism of alveolar cleansing from inhaled contaminants, schematically shown in Fig. 1.

Particle transport on the deformable ALI in the presence of LS material was demonstrated in vitro in the Langmuir trough experiments supplemented by mathematical modeling [9•,10]. These results revealed that compression of the liquid surface which contained a phospholipid monolayer, produced $\nabla\gamma$ and – as a result – the unidirectional flow of the interfacial region of fluid. This flow was visualized by recording of the displacement of solid particles at the interface (Fig. 2). Surface deformation rate, which is a critical factor in the discussed effect, should be fast comparing to the rate of surface concentration equilibration due to diffusion of surfactant (to/from the subphase or across the interface). During oscillatory deformation of the ALI (contraction and expansion), the flow direction is periodically changed, and a net transport of upper layer of the fluid may be observed if surface tension variations are not fully symmetric. Such asymmetry is simultaneously reflected by surface tension hysteresis measured during oscillations of the surface area. The γ-*A* hysteresis, which is considered an important dynamic feature of the active LS [11], may be caused by several factors: (i) structural rearrangement of LS molecules at ALI, (ii) surfactant mass transfer between the interfacial region and the subphase, and (iii) the intrinsic mechanical properties of the ALI enriched in surface active-molecules [12••].

The γ-*A* hysteresis can be conveniently described on the grounds of surface dilatational rheology [13•], however the evaluated quantitative parameters, such as surface dilatational elasticity and surface dilatational viscosity, should be understood rather as the effective (apparent) than the absolute quantities since they usually depend on more factors than intrinsic mechanical properties of the ALI [12••]. Because the pattern of γ variation in the LS system is related to the efficiency of mass transfer phenomena in the alveolar region, alterations in the dynamic surface tension (including the hysteresis) in LS system can be considered as markers of undesirable physicochemical effects with the potential influence on health [14,15].

It is also supposed that LS plays an important physicochemical role in the non-ciliated parts of the bronchial tree. Assuming that a static surface tension gradient exists in the pulmonary bronchioles and small bronchi due to a non-homogeneous (i.e. decreasing) surface density of surfactant-producing cells, it can be postulated that this gradient produces the flow capable of displacing deposited particles towards larger bronchi [16•]. Then the deposits are pushed to the upper respiratory tract along the ciliated airways by, so called, "mucociliary escalator" [17•,18].

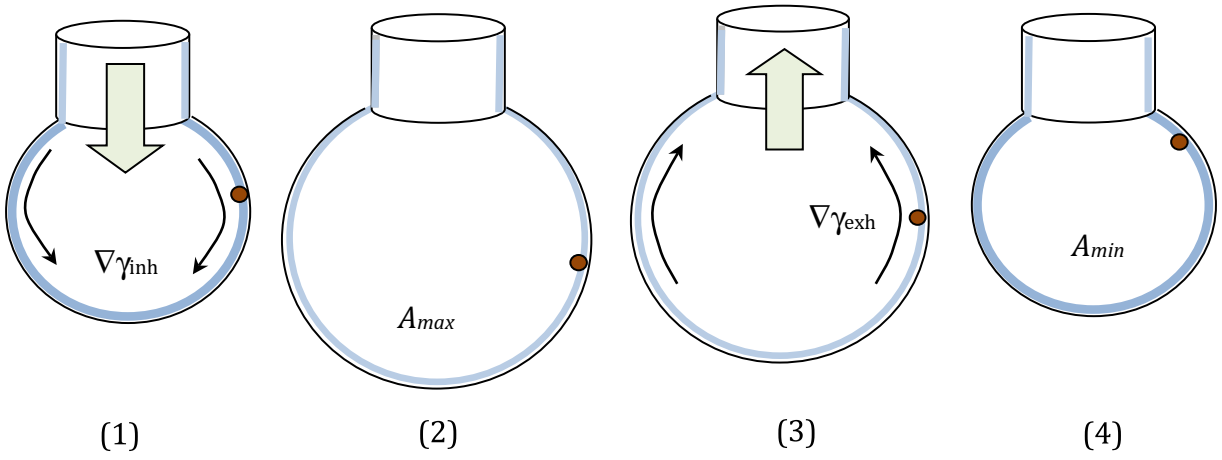

Fig. 1. Schematic flows of alveolar liquid during breathing cycle caused by surface tension gradients $\nabla\gamma$. Expansion of the surface area, *A*, during air inhalation (1) causes an increase of the surface tension, γ, inside the alveolus, so the liquid layer flows in. At the maximum inflation (2) γ is high and next starts to decrease as the air is drawn from the alveolus (3). This pushes the liquid out until the air exhalation ends (4). A deposited particle (represented by a dark dot) is effectively displaced towards alveolar exit to the pulmonary bronchiole at each cycle.