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Research Paper

Barrier or carrier? Pulmonary surfactant and drug delivery

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ABSTRACT

To consider the lung as a target for drug delivery and to optimise strategies directed at the pulmonary route, it is essential to consider the role of pulmonary surfactant, a thin lipid–protein film lining the respiratory surface of mammalian lungs. Membrane-based surfactant multilayers are essential for reducing the surface tension at the respiratory air–liquid interface to minimise the work of breathing. Different components of surfactant are also responsible for facilitating the removal of potentially pathological entities such as microorganisms, allergens or environmental pollutants and particles. Upon inhalation, drugs or nanoparticles first contact the surfactant layer, and these interactions critically affect their lifetime and fate in the airways. This review summarises the current knowledge on the possible role and effects of the pulmonary surfactant system in drug delivery strategies. It also summarises the evidence that suggests that pulmonary surfactant is far from being an insuperable barrier and could be used as an efficient shuttle for delivering hydrophobic and hydrophilic compounds deep into the lung and the organism.

1. Introduction

The discovery of new therapeutic agents includes the development of innovative drug delivery strategies that have the potential to overcome physiological barriers, avoid the side effects from drugs and control bioavailability. Over the last few years, an estimated 90% or more of the new drugs have been classified as class II or IV under the Biopharmaceutical Classification System (BCS), meaning they are poorly soluble in water [1]. Therefore, new strategies are needed to circumvent the drug solubility problem. Recently, drug encapsulation, the development of new nanodevices using surfactants or reduced particle size and the establishment of novel sites for drug entry have become important innovations.

Although the intravenous route is still a gold standard in drug application, the inhaled route presents several benefits and is starting to be considered as a promising alternative, in principle, for drug entry, not only for local but also for systemic treatments. Sophisticated devices for delivering inhaled drugs have recently been made available, yet this route for the administration of drugs had been used thousands of years ago in ancestral techniques such as burning and inhaling aromatic and medicinal plants [2,3]. Administering drugs directly through the airways is a non-invasive route for local and systemic delivery and often allows for a reduction in the drug dosage [4]. Active molecules are expected to have a rapid onset of action and reach a high local concentration once delivered through the lung [5].

The respiratory surface possesses other important advantages that facilitate drug absorption. It has a large surface area (approximately 100 m^2 for a human adult), and typical features of the thin alveolar epithelium coating the inner surface of the lungs include high permeability and significant vascularisation. Additionally, the low alveolar enzymatic activity results in a very slow clearance of both drugs and nanoparticles, compared to other ways of administration [3,6]. Therefore, the absorption and bioavailability of different types of molecules are considerably better than when they are delivered through conventional methods (oral, topical or injected) [4], especially for poorly water-soluble drugs. As a result, the dose and dosing frequency could be reduced, ultimately yielding an easier and more patient-friendly delivery route, especially for those who suffer from chronic lung diseases.

Nevertheless, to consider the lungs as a target for drug delivery and to optimise strategies directed at the pulmonary route, it is necessary to consider the different layers and barriers that the drugs and nanosystems must cross, including the innate immune system, mucus, pulmonary surfactant, interstice, epithelium and endothelium. The reasonable clearance at which inhaled particles are exposed also needs to be considered [7].

This review mainly focuses on the possible role and effects of the pulmonary surfactant system on pulmonary drug delivery strategies. It will also summarise the evidence that suggests that the pulmonary surfactant is far from an inconvenient barrier and

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could act as an efficient shuttle for delivering hydrophobic and hydrophilic compounds into the lung and the organism. To better understand the possibilities for pulmonary surfactant as a carrier system, this review will first address the main characteristics of the respiratory system and the importance for the vehiculisation of drugs.

2. An ancient approach as for novel therapeutic strategies

The respiratory system is the responsible for capturing O_2 from the environment and clearing CO_2 produced by cellular metabolism. All terrestrial animals, adult amphibians and lungfishes breathe air from the atmosphere using very complex structures, the lungs. In addition to the respiration process, the lung establishes a significant barrier that protects the respiratory system from the entrance of external noxious agents such as particles and various pathogenic microorganisms. It is therefore necessary to properly understand the functions, anatomy and physiology of the respiratory system when considering pulmonary drug delivery.

In mammals, the lung is a branching organ composed of tubes that progressively subdivide from the conducting regions into the respiratory zone, reaching a total surface of approximately 100 m^2. The conducting regions include the nasal cavity, nasopharynx, trachea, bronchi and terminal bronchioles, whose main function is to move air into and out of the lung; the respiratory zone comprises the respiratory bronchioles and the air sacs or alveoli, which are involved in gas exchange between the atmosphere and the bloodstream. In humans, 23 bifurcations occur from the trachea to alveoli, decreasing the diameter (until approximately 200 μm) and the wall thickness (until approximately 0.1–0.4 μm in the alveoli) of the airways [6]. The thin alveolar epithelium facilitates the diffusion of small entities from the external environment to the interior media. However, the progressively reduced diameter of the airways complicates drug deposition in deep lung regions because the smaller the diameter of the tubes the smaller the aerodynamic diameter of the particles with the capability to reach the deep lung [7].

In addition to the geometry of the lungs, the entrance of foreign microorganism and substances is prevented by the respiratory surface, which comprises several structured layers. The conductive regions are mostly lined by ciliated and club cells and are covered by a thick mucus layer with an aqueous hypophase, which is responsible for trapping and clearing detrimental compounds. The respiratory zone is a very thin multilayer region covered by a tiny aqueous layer, coated by pulmonary surfactant, a lipid–protein surface active material. Under the aqueous film, a cell monolayer is located, which is mostly composed of type I pneumocytes (up to 90% of the surface), whose main functions are gas exchange and protein and ion transport. This monolayer also contains type II cells, which synthesise the pulmonary surfactant [6,8]. There is also an interstitial layer with endothelial cells, which form the blood and lymphatic capillaries. Other additional barriers include immunological agents, epithelial tight junctions and blood plasma.

3. Why should we vectorise drugs?

When drugs are inhaled, they have to overcome different barriers before reaching the target location. Therefore, diverse strategies have to be developed to facilitate the entrance of active molecules into airways, while extending their retention time and having the drug released progressively at therapeutic levels. Novel formulations based on generating insoluble complexes and clustering the drug into nanometre-size defined particles are being explored to administer corticosteroids, sex hormones and insulin. Several structures and sophisticated micro- and nano-vehicles have been studied for more than 30 years to address these types of challenges. Drug vehiculisation, vectorisation or encapsulation aim to (i) protect drugs from degradation, (ii) increase the adsorption and cellular penetration rates, (iii) control the drug distribution to increase efficacy and decrease side-effects and/or (iv) improve diagnostic imaging techniques.

These vehicles could be functionalised to (i) increase their biological half-life (e.g., coating with PEG), (ii) target defined locations in the body, using specific ligands or monoclonal antibodies, (iii) allow drug release under particular physiological or pathological conditions, (iv) avoid lysosomal degradation once the carrier enters the cell and/or (v) engineer multifunctional nanosystems [9]. In general, every nanocarrier to be administered through the lungs should be biocompatible, biodegradable, inhalable and considerably stable against aerosolisation forces, and it should also possess high drug uploading capacity [4].

Several approaches are currently in preclinical and clinical trials, including polymeric carriers, lipid nanosystems and dendrimers. The pulmonary surfactant, which has historically been considered a barrier, could be a promising strategy for transporting various drugs and nanocarriers efficiently. The potential for using pulmonary surfactant as a drug delivery system has recently gained attention. It provides advantages because it can solubilise and transport poorly water-soluble drugs along the entire respiratory surface, while protecting them from other barriers, due to its lipid composition and spreading capabilities.

4. The pulmonary surfactant system: a promising approach for transporting drugs

Since 1929, when Kurt von Neergaard suggested the existence of a surface active material in the lungs, which was confirmed 25 years later by Richard Pattle in England and John Clements in the USA, several studies have been carried out to investigate its composition, structure and function, as well as the disorders related with its dysfunction or deficiency [10]. Various surfactant formulations, obtained from porcine and bovine sources or even from synthetic sources, have been developed to treat preterm new-borns. In addition to surfactant replacement therapies, new surfactant-based therapeutic advances are currently being investigated, including new procedures for PS administration (e.g., aerosolisation or nebulisation) or its use as a drug delivery system [11,12].

Due to its unique biophysical properties, which will be explained further below, the pulmonary surfactant system has the capability to very rapidly (within a few seconds) adsorb into the lung air–liquid interface and, once there, to efficiently spread along it. Additionally, because the pulmonary surfactant system is mainly composed of lipids, it offers a perfect hydrophobic environment to solubilise various poorly water-soluble molecules. The ability of surfactants to dramatically reduce the surface tension in a water solution also stabilises emulsions, preventing drug droplet aggregation [12]. Conversely, PS is not an effective agent for retaining hydrophilic substances because of its main lipid component, dipalmitoylphosphatidylcholine (DPPC), and the hydrophobic surfactant proteins (SP-B and SP-C), which influence membrane lipid packing and make PS a very dynamic and permeable complex [11,13–15]. Consequently, it is important to combine PS with carriers that could retain not only hydrophobic but also hydrophilic molecules, as they interact and travel with PS.

These unique surfactant properties could be exploited to deliver various drugs and nanosystems through the lungs in a very efficient manner. To better understand the therapeutic possibilities