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ORIGINAL ARTICLE

Fundamentals of pulmonary drug delivery

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Abstract

Aerosol administration of peptide-based drugs plays an important role in the treatment of pulmonary and systemic diseases and the unique cellular properties of airway epithelium offers a great potential to deliver new compounds. As the relative contributions from the large airways to the alveolar space are important to the local and systemic availability, the sites and mechanism of uptake and transport of different target compounds have to be characterized. Among the different respiratory cells, the ciliated epithelial cells of the larger and smaller airways and the type I and type II pneumocytes are the key players in pulmonary drug transport. With their diverse cellular characteristics, each of these cell types displays a unique uptake possibility. Next to the knowledge of these cellular aspects, the nature of aerosolized drugs, characteristics of delivery systems and the depositional and pulmonary clearance mechanisms display major targets to optimize pulmonary drug delivery. Based on the growing knowledge on pulmonary cell biology and pathophysiology due to modern methods of molecular biology, the future characterization of pulmonary drug transport pathways can lead to new strategies in aerosol drug therapy. © 2003 Elsevier Science Ltd. All rights reserved.

doi: 10.1053.rmed.2002.1457, available online at http://www.sciencedirect.com

Keywords airways; drug; aerosol; transport.

INTRODUCTION

In addition to their prominent role in the regulation of the airway tone and the production of airway lining fluid, the respiratory epithelial cells display an important barrier between higher organisms and their environment which can be used for pharmacological interventions. In this respect, the large surface area of approximately 70–140 m^2 in adult human lungs can be efficiently used for the aerosolic administration of a large variety of drugs. The topical administration of non-peptide and peptidomimetic drugs already plays an important role in the treatment of various pulmonary and systemic diseases and on the basis of new knowledge on distinct transport systems (1,2) aerosolic drug delivery may be optimized and is reaching a higher bioavailability.

Received 12 September 2002, accepted in revised form 1 October 2002
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TOPICAL AND SYSTEMIC DRUGS AND COMPOUNDS

A general distinction between topical and systemic compounds has to be made: for the aerosolic administration of topical, respiratory drugs, a large number of substances already exists encompassing different classes of asthma(3), antimicrobial (4) and pulmonary antihypertensive therapeutics (Table 1) (5).

Also, a large number of reports on the pulmonary delivery of systemic drugs exist. In this respect, different non-peptide and peptide-based drugs such as insulin (6–8), human growth hormone (9) and oxytocin have been reported to reach the systemic circulation following aerosol administration (Table 2).

With regard to the most socio-economically most important systemic compound, insulin, recent studies have addressed the optimization of the delivery process. Using human monocomponent insulin in lyophilized dextran starch microspheres, a bioavailability of 30% was achieved after administration to the nasal cavity of rats with peak insulin concentrations within 7–10 min and a

Table 1. Examples of aerosol drugs for topical treatment of pulmonary diseases (except obstructive diseases)

Class	Drugs	Diseases
Antimicrobial	Aminoglycosides Penicillins Pentamidine	Cystic fibrosis Bronchiectasis AIDS
Antiviral	Ribavirin	RS-virus-infections
Vaccines	Viral/bacterial	Infectious diseases
Immunosuppressive drugs	Steroids	Lung fibrosis
Surfactant		ARDS/IRDS
Protease	Trypsin	Alveolar proteinosis
Prostaglandins		Primary pulmonary hypertension

Table 2. Examples of aerosol drugs for systemic treatment

Drugs	Diseases
Insulin	Diabetes
Heparin	Anticoagulation
Ergotamine	Headache
Calcitonin	Osteoporosis

maximal decrease in glucose blood concentration after 20–30 min.

As the relative contributions from the large airways to the alveolar space are important to the local and systemic availability, the sites and mechanism of uptake of the different target compounds have to be characterized. Among the different respiratory cells, the ciliated epithelial cells of the larger and smaller airways and the type I and type II pneumocytes are the key players in pulmonary drug transport. With their diverse cellular characteristics, each of these cell types displays unique uptake characteristics.

CELLULAR ASPECTS OF PULMONARY DRUG TRANSPORT

The transepithelial transport of compounds along the respiratory epithelium from the upper airways with nasopharynx, trachea and large bronchi to the lower respiratory tract with small bronchioles and alveoli is characterized by large quantitative differences. In this respect, the transport in the upper airways is limited by a smaller surface area and lower regional blood flow. Also, the upper airways possess a high filtering capacity and remove 70–90% of pressurized particles. In contrast, the smaller airways and alveolar space account for more than 95% of the lung's total surface area(10). Also, this compartment is directly connected to the systemic circulation via the pulmonary circulation.

There are two major cell types found in the alveolar epithelium: type I and type II pneumocytes. Whereas type I cells have a very thin cell body with long membranous extensions, occupying an area of about 95% of the alveolar surface(11), the type II pneumocytes are characterized by a more cuboidal morphology and cover about 5% of the total alveolar surface (12,13). Studies on the subcellular morphology of type I cells revealed the presence of endocytotic vesicles which may function as carriers in the absorption processes of larger proteins such as insulin (5.7 kDa) (14,15). Although type II pneumocytes express a variety of transport proteins (1,2), it is generally accepted that their main functions are the production of surfactant proteins and the differentiation into type I cells after epithelial barrier injuries.

The pulmonary blood–gas barrier consists of a thick and a thin side, which are composed of the alveolar epithelium, the capillary endothelium, and the intervening extracellular matrix (basement membranes of the two cell layers)(16).

Out of the two cell types involved in the blood–gas barrier, the type I cells display most likely the rate-limiting step concerning the uptake of compounds into the pulmonary circulation as previous studies reported a 10^3 times lower permeability for substances such as sucrose in comparison to endothelial cells (17). This is based on the difference in pore size between alveolar cells (0.6–1 nm) and endothelial cells (4–5.8 nm) (18)and the tight junctions depth which is $0.261 \pm 0.023\ \mu m$ (significantly) higher than the tight junctions depth of the capillary endothelial cells ($0.166 \pm 0.011\ \mu m$)(19).

In contrast to these conditions at the blood–gas barrier, three other different types of tight junctions have been identified for extra- and intrapulmonary airways(20). Most importantly, they differ in the degree of luminal fibril interconnections which are sparsely interconnected in type I, more densely interconnected in type II and most densely interconnected in type III tight junctions. While the type I is almost exclusively found between extrapulmonary airway ciliated cells, the type II is primarily present in smaller airways and between Clara cells and the type III between mucous cells (20) with a secretory cycle-associated change in permeability.

This dependence upon the secretory cycle, which is leakier when the mucous cells are in a state of active secretion has also been reported for other cell types such as mammary gland epithelial cells (21,22). It is most likely

that the regional differences in tight junction morphology are directly linked to the transepithelial transport capacities of water and ions in contrast to actively transported larger molecules.

AEROSOL ADMINISTRATION AND DEPOSITION

There are two primary modes of pulmonary aerosol administration: nasal and oral inhalation. As the nasal inhalation is limited by anatomical features such as a narrower airway lumen, oral inhalation of compounds is generally preferred. In this respect, previous studies demonstrated (23,24) a far better oral inhalative administration of 5 μm diameter particles with a concentration loss of only 20% in comparison to 85% by nasal administration.

The three principal mechanisms which lead to pulmonary deposition are inertial impaction, sedimentation and diffusion. The inertial impaction occurs during the passage through the oropharynx and large conducting airways if the particles possess a certain mass and velocity. Inertial impaction can be partially influenced by hyperventilation and does not occur when particles have a diameter below 3 μm. These particles are subject to sedimentation by gravitational force which occurs in smaller airways and is influenced by breath-holding. From a range below 0.5–1 μm, particles are deposited by diffusion which is based on the Brownian motion (25–27).

There are different parameters with a crucial influence on the site, extent and efficacy of specific deposition of aerosolic drugs. Next to morphological aspects and ventilatory parameters (26,28), the aspect of particle/droplet size and geometry is most important. Within this area, there are numerous factors with an influence on the deposition, including particle size (diameter), density, electrical charge, hygroscopy, or shape (i.e. fibers) (25,29,30). Also, deposition is influenced by the particle source which can be a solution, powder or suspension (26,27). In this respect, it was demonstrated that solution-based aerosols were characterized by 2-μm mass-median aerodynamic diameter (MMAD) particles whereas suspension-based aerosols displayed 4-μm MMAD particles (31). The particle size is commonly expressed as the aerodynamic diameter, which is a variable depending on the shape, density and size of the object. If aerosols contain different particles, the size distribution is usually characterized by the MMAD. A maximal alveolar deposition is reached with particle sizes of 3 μm and an increase of the MMAD leads to an inertial impaction-based shift in deposition in larger airways. In this respect, the oropharyngeal deposition of an 8-μm particle has a probability of about 50%, whereas it reaches approximately 100% for a 16-μm particle (32).

Also, hygroscopic characteristics can influence the deposition and due to the high levels of relative humidity, reaching about 44 $\mu g/cm^3$ in the alveolar lumen, particles may be subject to changes in size. In this respect, depending on water content and airway tonicity, hypertonic particles can increase in size by hygroscopic growth with a consecutive change in deposition towards larger airways (33).

Major ventilatory parameters with impact on the particle deposition are breath pattern, flow rates and tidal volume and there can be large inter-and intraindividual variations in these parameters. As an example, breath-holding for 5–10 s on completion of inhalation, a low flow rate (less than 20 l/min), and an increase in the inhaled volume can lead to an increase in particle deposition, especially for particles with a diameter around 0.5 μm which are subject to sedimentary deposition (34–36). In contrast, low flow rates of 15 l/min can lead to an increase in large conductance airway deposition of >3 μm particles due to inertial impaction (37) and also, rapid inhalation together with a high respiratory rate increases inertial impaction of particles in the large airways (38).

DELIVERY DEVICES

Although there is a large number of devices (39,40) which can be used to generate particles (Table 3), the most common systems are nebulizers, metered dose inhalers (MDIs) and dry powder inhalers (PDIs).

Table 3. Devices for generating particles

Device	Particle size (μm)	Particle size uniformity
Metered-dose inhaler	1–35	Heterogeneous
Jet nebulizer	1.2–6.9	Heterogeneous
Ultrasonic nebulizer	3.7–10.5	Heterogeneous
Spinning disc	1.3–30	Monodisperse
Dry powder	Flow-related	Heterogeneous
Vibrating orifice	0.5–50	Monodisperse
Condensation	1.1	Monodisperse
Solid particle	0.1–4	Heterogeneous/monodisperse

The currently available standard inhalation devices generally produce aerosols which are heterodisperse in size. Although monodisperse particle-sized aerosols are better specifically targeted to the lower airways, the production of these is largely limited by complex and expensive generation processes such as vibrating orifice, spinning disc method or electrostatic precipitation (40,41).

PULMONARY CLEARANCE OF AEROSOL-ADMINISTERED DRUGS

There are two major clearance pathways for substances which are transported across the respiratory epithelium: the mucociliary system and alveolar macrophages. Whereas the mucociliary system is bound to the larger airways, the macrophages are found both in the alveolar space and along larger and smaller airways.

Mucociliary clearance

The mucociliary clearance displays an integrative function of beating cilia and lining fluid with the two main purposes of trapping and transporting airborne particles.

Ciliated epithelial cells cover 30–65% of the airway epithelial cells in the human respiratory tract, and each ciliated cell houses about 200 cilia of 5–6 μm length at a density of 6–8 μm^{-2}(42). Parallel to the decrease of mucociliary transport activity as the airways become smaller, the distribution of ciliary epithelial cells changes and the percentage decreases from 53% in the trachea to 45% in the first airway generation, to 15% in the fifth airway generation(43).

The lining fluid is composed of the periciliary fluid, a lubricating layer surrounding the cilia, the viscous layer of mucus and the gel layer. Transport through these layers is functionally distinct as they consist of different components such as soluble and gel-forming mucins which can be altered in their composition in disease (44,45).

The mucociliary clearance rate, which can be used as an outcome measure for potential therapeutic agents, is about 10 mm/min in the trachea of normal individuals(46). The clearance rate can be examined indirectly as ciliary beat frequency (47) or directly as the rate of removal of marker substances. The ciliary beat frequency and mucociliary transport are generally well correlated (48) and the beat frequency can be assessed *in vivo* and *in vitro* (49–51).

ALVEOLAR CLEARANCE

Aerosol particles which have been deposited in the alveolar space and terminal airway units can be subject to absorptive or non-absorptive removal processes. Whereas the nature of non-absorptive transport processes of particles from the terminal airway units to the airways with mucociliary clearance activity has not been fully elucidated so far, the absorptive removal processes involves uptake by macrophages and epithelial cells(52). The adhesion of airborne particles to alveolar macrophages is mediated through electrostatic interaction or receptor mediation and particles are then internalized through surface cavitation, or vacuole and pseudopod formation(53). Depending on the nature of the particles, internalization is followed by further metabolization or digestion by peptidases in case of proteins (52,54).

Activated macrophages may then secrete a variety of cyto-and chemokines and migrate to the ciliated airway epithelium for transport via mucociliary clearance or penetrate through the respiratory epithelium into the interstitial tissue(13).

The internalization of airborne particles depends on the particle size and composition of coating material. Both features can be used to selectively control drug uptake by alveolar macrophages. While particles of 3 μm diameter are far better internalized than particles with 6 μm, a diameter of less than 0.26 μm prevents from macrophageal phagocytosis (55–57).

The diversity of the clearing processes can be illustrated by the deposition of radio-labeled aluminosilicate particles of diameter sizes 1.2 and 3.9 μm, which was shown to be a triphasic process with half-lives of approximately 1, 20 and >300 days. These phases were suggested to correspond to the processes of mucociliary clearance, alveolar macrophages clearance and alveolar epithelium penetration(58).

CONCLUSION

Pulmonary administration of drugs plays an important role in the treatment of various respiratory and systemic diseases and displays an attractive area of future drug development. The effects of an aerosol-based drug are dependent on a variety of factors: starting from the nat-

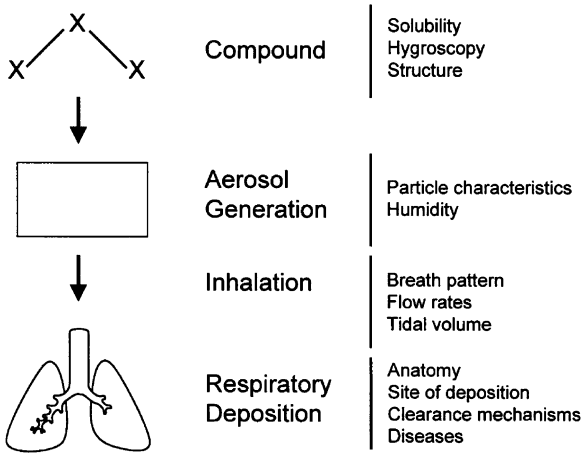

Fig 1. Influencing factors on the pulmonary delivery of drugs.

ure of the compounds, cellular aspects, characteristics of delivery systems and aerosol administration to deposition in pulmonary clearance mechanisms (Fig. 1), multiple ways to manipulate drug delivery exist.

An optimal delivery system would specifically deposit the drug at its pulmonary target region, independent of ventilatory or pathophysiological parameters. To optimize current delivery systems, future studies addressing the unique molecular, biochemical, and physiological characteristics of various respiratory regions have to be carried out applying modern techniques of molecular biology(59), morphology (60,61) and physiology (62,63).

Acknowledgements

We thank J. Springer and F. Döring for helpful discussions. This study was supported by the European Union (Biomed 2, EUBMH4CT960569), the German Academic Exchange Service (DAAD, D/00/10559), and the Ministry of Education and Research (BMBF 01 GC 0002).

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