REVIEW ARTICLE

Absorption of higher-molecular-weight substances via the lung

Peter von Wichert

Division of Respiratory and Intensive Care Medicine, Department of Medicine, Philipps University of Marburg, Germany

KEY WORDS

absorption, drug uptake, liquid balance, lung, proteins

ABSTRACT

Inhalation is now increasingly used as a route of drug administration, both small- and high-molecular-weight substances, although the scientific understanding of the mechanisms of their absorption is rather limited. The present review summarizes the mechanisms of absorption of higher-molecular substances through the pulmonary epithelium with the aim to draw attention to this issue.

Introduction The exchange between the environment and the human body occurs either through absorption of foreign substances or secretion of endogenous substances. Absorption occurs primarily in the intestine but also via the skin, whereas excretion involves the kidney, bowel, and, in some cases, the skin. It is often overlooked that the lung with an epithelial surface of 80 m^2, with nearly 70 m^2 being in contact with the capillaries,[1] is particularly exposed to the environment. The lung is typically viewed as an organ for gas exchange, although gas exchange already comprises absorption and excretion. For a long time, inhalation has been used as a way of drug application to the lung as in asthma therapy or to the systemic circulation as is the case of smoking. The capacity of the lung to absorb substances, i.e., the nonrespiratory function of the lung,[2] is gaining increasing interest because not only small-molecular-weight drugs are absorbed but also high-molecular-weight substances, such as proteins, may reach the systemic circulation via the lung.[3-7] The administration of drugs of higher molecular weight is a more recent approach to systemic therapy, although initiated long ago by Gänsslen.[7] These questions are of clinical interest. One example of pulmonary high-molecular drug delivery is the successful use of inhaled insulin to treat diabetes.[5,8-11] Although it is not very effective in daily practice, the approach clearly shows certain possibilities. Many other approaches have been investigated[12,13] or may be developed in the near future.

The present review provides some information concerning the physiological and pathophysiological mechanisms of absorption of higher-molecular-weight substances via the lung, although the scientific background is still limited.[6] In the past few years, several reports have tried to elucidate the absorptive function of the lung to understand the mechanisms involved in the therapeutic use of drugs administered via the lung.[4,9,12-14]

This paper aims to raise open questions concerning the absorption of substances via the lung, but it is not intended to discuss the methods of inhalation or methods to measure the uptake of labeled substances. Moreover, the review does not cover the measurement of the permeability of the lung tissue and different epithelial cells, i.e., the alveolar or bronchial epithelium. The alveolar and bronchial epithelium is able to absorb drugs and proteins separately, but data on the exact amount of drug absorbed via the lung related to bronchial or alveolar tissue are still lacking. In pharmaceutical studies, the lung has often been regarded as a passive membrane. The biological questions relating to the absorption of substances and the cellular mechanisms facilitating absorption have only rarely been addressed, although it is most likely that the lung epithelium is not a passive membrane. The anatomical and functional conditions within the lung[1,15,16] comprise the conditions of permeability. The different cell types encountered from air to blood, the ventilation and the perfusion of the lungs are the prerequisites for the absorption of a given substance. It is currently impossible to analyze these different influences separately in relation to the absorption of different drugs, but changes in pulmonary

Correspondence to:
Prof. Dr. Peter von Wichert,
Deptartment of Medicine,
Philipps University of Marburg,
Eppendorfer Landstr. 14,
D-20249 Hamburg, Germany,
phone: +49-40-46-856-220,
fax: +49-40-46-856-220,
e-mail: vonwichert@t-online.de
Received: April 16, 2012.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012;
122 (Suppl 1): 78-83

TABLE 1 Examples of established administration of systemic drugs via inhalation

nicotine
bronchodilatating drugs (ß-adrenergic and vagolytic drugs)
cromones
corticosteroids
cannabis
cocaine
adrenaline
anesthetic gases

structure and function will have a profound effect on drug absorption.

It is well known that inhalation of particles, chemicals, or biological substances may induce immune reactions in the lung, as is the case in asthma or alveolitis. The issue of immunological processes induced by the presence of foreign substances in the peripheral lung will not be dealt with in this paper, particularly because there is a paucity of detailed studies investigating the administration of immunogenic drugs via the lung.

A short overview of low-molecular substances It is well known that some low-molecular-weight substances are extremely well absorbed in the lung, e.g., nicotine and other addictive substances. However, β-adrenergic drugs, derivates of atropine or steroids, and other therapeutic drugs are also absorbed in the lung (TABLE 1). Interestingly, the dosage given via inhalation route often corresponds to an intravenous dosage, even if local effects on the lung are not intended.[17] Active transport via the cell membrane (e.g., through receptor binding) has been suggested, but a concentration-dependent passive transfer via the membrane also has to be considered. Unfortunately, there are only scanty data on the mechanisms of these biological processes, although some drugs, e.g., β-adrenergic drugs or steroids, are regularly administered via the lung. Low-molecular-weight substances may also be transported transepithelially in solution form; therefore, attention should be paid to the water balance across the alveolar epithelium. Concerning the difficulties to understand the absorption of low-molecular-weight substances across the lung epithelium, it becomes clear that dealing with high-molecular-weight substances will raise a lot more complex questions.

Absorption of high-molecular-weight substances The absorptive capacity of the lung for high-molecular-weight substances has been known for the past few decades.[7,10,13,18,19] Presently, the role of peptides and proteins draws considerable attention since the successful administration of insulin via the inhalation route has raised a number of new questions. Irrespective of the specific effects of inhalation therapy with a biologically active substance, i.e., a hormone such as insulin,

TABLE 2 Examples of systemic administration of higher-molecular-weight drugs via the lung: studies in animals or humans; mainly experimental studies

heparin	erythropoietin
interferon-α, -β	calcitonin
insulin	α-1-proteinase inhibitor
human growth hormone	antibiotics
FSH	glucagon
TSH	prolactin
parathyroid hormone	GCSF
luteinizing hormone	oxytocin
vasopressin analogues	cyclosporine A
somatostatin	morphine and derivates

This list is not complete; it is only given to show the broad spectrum of substances that are attempted to be administered via the lung by inhalation[4-6,10,21,22,38,46,47]

Abbreviations: FSH – follicle-stimulating hormone, GCSF – granulocyte colony-stimulating factor, TSH – thyroid-stimulating hormone

a series of questions have to be addressed here because the biological mechanisms of absorption are particularly important. These questions have also been addressed in reviews published during the last years.[3-5,7,8,13,20-22] Of note, most of these data are experimental but they demonstrate the scientific power behind these questions and provide a strong stimulus for further research in this field. Only few clinical data are available and to mention the results of some studies does not mean that clinical application will soon follow. The examples of these studies are provided in TABLE 2.

Absorption of lipids The absorption of lipids is essential in the recycling of surfactant[23] and follows mainly the binding to receptors.[24] Binding proteins of those receptors have been characterized.[25] Recently, phospholipid transport proteins have been described, but the function has not been completely elucidated.[26] Lipid absorption has been described in detail in previous studies.[20,27,28] Those lipids may serve as vehicles for lipophilic drugs. At present, there are no regular approaches to administer lipophilic drugs via the lung. In contrast, liposomes have been used as transport vehicles to administer interleukin 2 and cyclosporine A. Also, a study with inhaled insulin-containing liposomes has been published.[29]

Absorption of proteins There are different mechanisms by which higher-molecular substances may pass the pulmonary epithelium (TABLE 3). In the gut, proteins are continuously subject to degradation, whereas the lack of proteolytic capacity in the lung almost excludes these processes. Nevertheless, some proteolytic activity may be observed in the lung or in bronchial secretions,[5] at least by the presence of leukocytes and macrophages, which are usually present in the lung. The lung contains protease inhibitors, but there

TABLE 3 Mechanisms of protein absorption in the lung

degradation
transcellular transport
– pinocytosis
– internalization via receptors
paracellular transport

is scarce knowledge about the interactions of these compounds with proteins during the absorption of proteins via the alveolar wall. Current research will certainly create a rising number of protein drugs. Therefore, their administration via the lung is of increasing scientific and economical interest,[5] and there is an urgent need to address these mechanisms in a more comprehensive way. So far, data are only available for a limited number of peptides or proteins from a few experimental studies mostly on small mammalians.

The reuptake of albumin, which might possibly reach the alveoli in lung edema, has been repeatedly investigated and is summarized in a recent review by Hastings et al.[20] It has been shown that albumin is taken up by endocytosis in type-I and type-II cells. According to the present knowledge, lung epithelium, in contrast to other epithelial barriers, facilitates the clearance of intact proteins without degradation, thus drawing attention to the administration of drugs via the lung. The clearance of proteins is much slower than liquid clearance[30] and depends on the molecular size[31] and protein concentration in the alveolar space. A receptor-mediated transcytosis mechanism at low protein concentration will change to a passive paracellular mechanism at higher concentrations.[20] Specific receptors for endocrine active peptides, e.g., vasoactive intestinal peptide, gastrin or surfactant protein A, accelerate the clearance, but there are only limited data concerning receptors for other drugs or proteins. Apart from the uptake of proteins via endocytosis,[32-35] there may be other pathways enabling the uptake of different substances.[36] It is still under discussion whether different mechanisms of protein and peptide absorption depend on the protein itself or whether the quality of the pulmonary epithelial tissue plays the critical role. Nonetheless, an association between the uptake and molecular size has been shown.[19]

Using A 549 cells, Kobayashi et al.[37] studied the permeability of 14 different peptides, and in agreement with previous studies they found that permeability depended on the molecular weight. Moreover, they showed a small but nevertheless significant degradation by proteases, but no dependence on temperature. The authors explained their findings with a paracellular uptake of the proteins investigated. The exact mechanisms and the forces counteracting oncotic pressure have not yet been resolved and have only rarely been analyzed. Recent studies[38,39] have shown active absorption of an oligopeptide (β-lactam antibiotic) by a peptide transporter, which was present in type-II cells, in the bronchial epithelium and in the endothelium of small arteries, but not in type-I cells. The role of other transporter proteins such as P-glycoprotein[40] or multidrug-resistant protein on absorption requires further evaluation. Whether this uptake mechanism also applies to high-molecular-weight proteins or to drugs has not been determined yet. Although most of the experimental results derive from isolated alveolar cells, it has to be stressed that the data for low- as well as for higher-molecular-weight substances do not differentiate between transfer across the alveolar wall and that across the bronchial epithelium, although from a practical point of view this would be extremely important in terms of different inhalation techniques and different therapeutic approaches.[41] An interesting approach is the use of absorption enhancers to facilitate the uptake of higher-molecular drugs.[42,43]

Effect of lung diseases on absorption The uptake of high-molecular-weight substances under pathological conditions has not been sufficiently assessed and still has to be elucidated, both for experimental and clinical settings. Known drug transporters, which play an important role during the intestinal absorption of pharmacological agents, have not been demonstrated in the lung so far. Nevertheless, such crucial information would be very helpful for the administration of therapeutic drugs, particularly proteins delivered by inhalation. For lower-molecular-weight substances, e.g., vitamin E, an increased uptake under hyperoxic conditions has been shown,[44] but for proteins there are virtually no data answering these questions. Unfortunately, we are not able to draw a convincing pattern concerning the changes in the absorptive capacity in the lung under pathological conditions. The studies dealing with the resolution of pulmonary edema do not address drug absorption in disease states. Apart from the technical problems encountered regarding the administration of drugs or substances, it is possible that every single disease of the bronchi or the lung affecting lung mechanics, which also have effects on the metabolism and changes in the cell composition of the lung tissue, decreases or increases the absorption of a given drug given via the inhalation route unexpectedly (TABLE 4). It should be noted that in the current literature basically nothing is known about these questions, particularly regarding pulmonary pathologies, although the issues have been mentioned in a number of reviews.[7,4,5,12,21,41,45]

Conclusion Since future drug development will certainly try to use the attractive possibility of drug administration via the lung,[45] from a clinical point of view there is an increasing need to elucidate the precise mechanisms of drug absorption under pathologic conditions.[23] This research should be done in experimental settings such as cell cultures as well as in experimental animals

TABLE 4 Factors that influence the administration and absorption of substances via the lung

administration systems
technique of breathing
breathing abnormalities
ventilation-perfusion imbalance
obstruction and inhomogeneous obstruction
mucus in the bronchi
alteration of alveolar cell composition – inflammatory cells in the alveoli – liquid in the alveoli – increased number of interstitial cells – interstitial fibrosis
alteration in the pulmonary circulation – inhomogeneous perfusion – role of bronchial circulation – vasculitis
alteration of the alveolo-capillary permeability – lung diseases – cardiac diseases – general diseases, e.g., systemic inflammation or sepsis
induction of immune reactions – by a drug or substance – by other mechanisms
interaction and interdependence of different substances or drugs in the lung

and clinical studies. The present paper aimed to draw attention to the problems related to drug inhalation and encourage future research to address these interesting and important questions. In addition, future studies may provide new essential insights into the function of the pulmonary epithelial barrier, which in turn could be of vital importance in the understanding of pulmonary diseases.

REFERENCES

1 Murray JF. The Normal Lung. Philadelphia, Saunders; 1976: 46.

2 Fishman AP. The nonrespiratory functions of the lungs. In: Fisman AP, ed. Pulmonary Diseases and Disorders. 2nd ed., New York, McGraw-Hill, 1988.

3 Edwards DA, Ben-Jebria A, Langer R. Recent advances in pulmonary drug delivery using large, porous inhaled particles. J Appl Physiol. 1998; 85: 379-385.

4 Gonda I. The ascent of pulmonary drug delivery. J Pharm Sci. 2000; 89: 940-945.

5 Gonda I. Systemic delivery of drugs to humans via inhalation. J Aerosol Med. 2006; 19: 47-53.

6 Agu RU, Ugwoke MI, Armand M, et al. The lung as a route for systemic delivery of therapeutic proteins and peptides. Respir Res. 2001; 2: 198-209.

7 Gänsslen M. Über Inhalation von Insulin. Klin Wochenschr. 1925; 4: 71.

8 Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. Nat Rev Drug Discov. 2007; 6: 67-74.

9 Wigley FM, Londono JH, Wood SH, et al. Insulin across respiratory mucosae by aerosol delivery. Diabetes. 1971; 20: 552-556.

10 Cefalu WT, Balagtas CC, Landschulz WH, Gelfand RA. Sustained efficacy and pulmonary safety of inhaled insulin during 2-years outpatient therapy (abstract). Diabetes. 2000; 49 (Suppl 1): A406.

11 Todo H, Okamoto H, Lida K, Danjo K. Effect of additives on insulin absorption from intratracheally administered dry powders in rats. Int J Pharm. 2001; 220: 101-110.

12 Groneberg DA, Witt C, Wagner U, et al. Fundamentals of pulmonary drug delivery. Respir Med. 2003; 97: 382-387.

13 Yu J, Chien YW. Pulmonary drug delivery: physiologic and mechanistic aspects. Crit Rev Ther Drug Carrier Syst. 1997; 14: 395-453.

14 Derendorf H, Hochhaus G, Mollmann H. Evaluation of pulmonary absorption using pharmacokinetic methods. J Aerosol Med. 2001; 14 (Suppl 1): 9-17.

15 von Hayek H. Die menschliche Lunge. [The Human Lung]. 2nd ed., Berlin, Springer, 1970. German.

16 Meyrick B, Reid L. The alveolar wall. Br J Dis Chest. 1970; 64: 121-140.

17 Sefrin P, Finkenzeller A. Endobronchial drug administration in resuscitation. Med Klin (Munich). 1991; 86: 20-23.

18 Ware L, Golden JA, Finkbeiner WE, Matthay MA. Alveolar epithelial fluid transport capacity in reperfusion lung injury after lung transplantation. Am J Respir Crit Care Med. 1999; 159: 980-988.

19 Bensch KG, Dominguez E, Liebow AA. Absorption of intact protein molecules across the pulmonary air-tissue barrier. Science. 1967; 157: 1204-1206.

20 Hastings RH, Folkesson HG, Matthay MA. Mechanisms of alveolar protein clearance in the intact lung. Am J Physiol Lung Cell Mol Physiol. 2004; 286: L679-L689.

21 Patton JS. Mechanisms of macromolecule absorption by the lungs. Adv Drug Deliv Rev. 1996; 19: 3-36

22 Siekmeier R, Scheuch G. Systemic treatment by inhalation of macromolecules – principles, problems and examples. J Physiol Pharmacol. 2008; 59 (Suppl 6): 53-79.

23 Foral PA, Malesker MA, Huerta G, Hilleman DE. Nebulized opioids use in COPD. Chest. 2004; 125: 691-694.

24 Ryan RM, Morris RE, Rice WR, et al. Binding and uptake of pulmonary surfactant protein (SP-A) by pulmonary type II epithelial cells. J Histochem Cytochem.1989; 37: 429-440.

25 Witt W, Kolleck I, Rüstow B. Identification of high density lipoprotein-binding proteins, including a glycosyl phosphatidylinositol-anchored membrane dipeptidase, in rat lung and type II pneumocytes. Am J Respir Cell Mol Biol. 2000; 22: 739-746.

26 Jiang XC, D'Armiento J, Mallampalli RK, et al. Expression of plasma phospholipid transfer protein mRNA in normal and emphysematous lungs and regulation by hypoxia. J Biol Chem. 1998; 273: 15 714-15 718.

27 Wright JR. Clearance and recycling of pulmonary surfactant. Am J Physiol. 1990; 259: L1-L12.

28 Young SL, Wright JR, Clements JA. Cellular uptake and processing of surfactant lipids and apoprotein SP-A in rat lung. J Appl Physiol. 1989; 66: 1336-1342.

29 Huang YY, Wang CH. Pulmonary delivery of insulin by liposomal carriers. J Contro Release. 2006; 113: 9-14.

30 Peterson BT, Griffith DE, Tate RW. Clearance of proteins from the air spaces following cardiogenic edema in sheep. Exp Lung Res. 1998; 24: 41-56.

31 Hastings RH, Grady M, Sakuma T, Matthay MA. Clearance of different-sized proteins from the alveolar space in humans and rabbits. J Appl Physiol. 1992; 73: 1310-1316.

32 Jones AT, Gumbleton M, Duncan R. Understanding endocytic pathways and intracellular trafficking: a prerequisite for effective design of advanced drug delivery systems. Adv Drug Deliv Rev. 2003; 55: 1353-1357.

33 Gumbleton M, Hollins AJ, Omidi Y, et al. Targeting caveolae for vesicular drug transport. J Control Release. 2003; 87: 139-151.

34 Williams MC. Endocytosis in alveolar type II cells: Effect of charge and size of tracers. Proc Natl Acad Sci U S A. 1984; 81: 6054-6058.

35 Matsukawa Y, Yamahara H, Yamashita F, et al. Rates of protein transport across rat alveolar epithelial cell monolayers. J Drug Target. 2000; 7: 335-342.

36 Auricchio A, O'Connor E, Weiner D, et al. Noninvasive gene transfer to the lung for systemic delivery of therapeutic proteins. J Clin Invest. 2002; 110: 499-504.

37 Kobayashi S, Kondo S, Juni K. Permeability of peptides and proteins in human culture alveolar A549 cell monolayer. Pharm Res. 1995; 12: 1115-1119.

38 Groneberg DA, Fischer A, Chung KF, Daniel H. Molecular mechanisms of pulmonary peptidomimetic drug and peptide transport. Am J Respir Cell Mol Biol. 2004; 30: 251-260.

39 Groneberg DA, Nickolaus M, Springer J, et al. Localization of the peptide transporter PEPT2 in the lung: implications for pulmonary oligopeptide uptake. Am J Pathol. 2001; 158: 707-714.

40 Ehrhardt C, Kneuer C, Laue M, et al. 16HBE14o-human bronchial epithelial cell layers express P-glycoprotein, lung resistance-related protein, and caveolin-1. Pharm Res. 2003; 20: 545-551.

41 Newhouse MT, Corkery KJ. Aerosols for systemic delivery of macromolecules. Respir Care Clin N Am. 2001; 7: 261-275.

42 Hussain A, Arnold JJ, Khan MA, Ashan F. Absorption enhancers in pulmonary protein delivery. J Control Release. 2004; 94: 15-24.

43 Morimoto K, Fukushi N, Chono S, et al. Spermined dextran, a cationized polymer, as absorption anhancer for pulmonary application of peptide drugs. Pharmazie. 2008; 63: 180-184.

44 Tölle A, Kolleck I, Schlame M, et al. Effect of hyperoxia on the composition of the alveolar surfactant and the turnover of surfactant phospholipids, cholesterol, plasmalogens and vitamin E. Biochim Biophys Acta. 1997; 1346: 198-204.

45 Lipworth BJ. Pharmacokinetics of inhaled drugs. Br J Clin Pharmacol. 1996; 42: 697-705.

46 Folkesson HG, Matthay MA, Weström BR, et al. Alveolar epithelial clearance of protein. J Appl Physiol. 1996; 80: 1431-1445.

47 Hamilton KO, Yazdanian MA, Audus KL. Contribution of efflux pump activity to the delivery of pulmonary therapeutics. Curr Drug Metab. 2002; 3: 1-12.

Wchłanianie substancji wysokocząsteczkowych przez płuca

Peter von Wichert

Division of Respiratory and Intensive Care Medicine, Department of Medicine, Philipps University of Marburg, Niemcy

SŁOWA KLUCZOWE

białka, płuca, przyswajanie leków, równowaga płynów, wchłanianie

STRESZCZENIE

Obecnie coraz częściej stosuje się inhalację do podawania leków składających się zarówno z małych, jak i z dużych cząsteczek, jednak naukowe wyjaśnienie mechanizmu wchłaniania tych substancji wciąż pozostaje niepełne. W pracy omówiono mechanizmy wchłaniania wysokocząsteczkowych substancji przez nabłonek płucny w celu zwrócenia uwagi na ten problem.

Adres do korespondencji:
Prof. Dr. Peter von Wichert,
Deptartment of Medicine,
Philipps University of Marburg,
Eppendorfer Landstr. 14,
D-20249 Hamburg, Niemcy,
tel.: +49-40-46-856-220,
fax: +49-40-46-856-220,
e-mail: vonwichert@t-online.de
Praca wpłynęła: 16.04.2012.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2012;
122 (Suppl 1): 78-83