Gaining the Upper Hand on Pulmonary Drug Delivery

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Abstract

Asthma, Chronic Obstructive Pulmonary Disease (COPD) and Cystic Fibrosis (CF) are all pulmonary diseases which are characterized by chronic inflammation and an increase in mucus production [1-3]. In CF, mutations in the CF transmembrane conductance regulator (CFTR) gene result in abnormal chloride secretion. This leads to dehydrated mucus and a failure of mucus clearance, making the airways prone to bacterial infections, chronic inflammation and chronic neutrophilia which result in pulmonary destruction and morbidity [4,5]. COPD and asthma have different underlying pathophysiology, with COPD representing an exaggerated inflammatory response to a chronic inhaled toxicant, usually tobacco smoke, and with asthma representing a genetic disposition to abnormal inflammatory responses to environmental stimuli such as dust mite allergens [6]. However, both the chronic bronchitis forms of COPD and asthma both present with mucus obstruction of the airways which can be fatal [7-10]. Excess mucus in the airways correlates well with disease pathophysiology such as a decline in lung function and prolonged bacterial infections [11-13]. At present there is no cure for any of these diseases. However, a number of treatment options such as inhaled antibiotics and mucolytic drugs are available to ease some of the respiratory symptoms. For the treatment of CF, oral CFTR correctors/potentiators that seek to pharmacologically correct common disease-causing CFTR mutations are being developed [14,15]. Asthma is typically managed with inhaled corticosteroids and β2 agonists [16]. Numerous potential therapies are also currently under development for COPD. In this mini-review, we discuss the delivery routes that are available for dosing the lungs, and the challenges encountered.

Systemic vs. Inhaled Delivery

Drugs to treat chronic respiratory diseases such as asthma, CF and chronic bronchitis have been available for many years and include both inhaled and orally administered compounds. When treating pulmonary diseases, there are several advantages of using inhaled drug delivery over systemic drug delivery; with inhalation, there is a rapid clinical response, systemic side effects are often minimized and inhaled drugs bypass barriers to therapeutic efficacy such as poor gastrointestinal absorption and first-pass metabolism in the liver [17]. Examples include inhaled antibiotics, corticosteroids, β2 agonists and mucolytics. Inhaled corticosteroids and beta agonists are the primary treatment for mild to moderate asthma as they can control asthma symptoms, improve lung function, and decrease the risk for exacerbations immediately as they reach the lungs quickly [18,19]. A downside to inhalation therapy is that the amount of drug delivered is limited by the efficiency of the device. Nebulizers deliver more drug than hand held inhalers but are time-consuming to the patient due to the compliance. As a case in point, CF patients spend more than 1h/day using a nebulizer, which has been suggested, is the limit of patient compliance [20,21].

In contrast, systemic drug delivery can be slower, there may be more off-target effects since the drug has better access to other organs, and a greater chance of the drug being metabolized/excreted before it can work on the lungs. Oral delivery is useful for patients with severe disease and the elderly who, due to technical difficulties, cannot properly use inhalers or nebulizers reliably and therefore may not receive the effective dose. Also, drugs with slow pharmacokinetics allow for sustained and higher drug concentrations in the lungs. For example, intravenous antibiotics are used to treat severe lung infections [22]. Oral steroids such as prednisone are often prescribed for severe asthma attacks and serve to dampen down lung inflammation. However, their systemic delivery can have numerous side effects including glucocorticoid resistance, fluid retention, increased blood pressure and mood swings [23-25].

Roflumilast is a type 4 phosphodiesterase inhibitor that is administered orally for the treatment of severe COPD. It is an anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with COPD and has been shown to improve lung function [26]. Since roflumilast is introduced orally, even though...
and nucleotide-based drugs being especially vulnerable to metabolism. In the absence of CFTR, Na⁺ absorption through the epithelial Na⁺ channel (ENaC) is enhanced in CF airways, which further contributes to mucus dehydration by depleting the airways of salt and water [50]. ENaC antagonism with inhaled amiloride was proposed as a remedy for mucus dehydration in CF airways. Amiloride blocks ENaC with submicromolar potency, but was originally designed as an orally-delivered diuretic. However, amiloride failed to have any impact on CF lung disease [51,52]. The reason for this is that amiloride has an extremely short half-life in the airways after inhalation. In vitro, when deposited on airway surfaces, the half-life was ~9 min [53], since amiloride is rapidly absorbed by organic cation transporters [54]. Given that amiloride is a diuretic, there is concern over its use as its rapid absorption through the respiratory tract may cause an effect on systemic sodium and potassium balance via actions on the kidney [55]. Indeed, intranasal installation of amiloride to mice caused them to lose ~10% of their body weight/day due to urine excretion [56].

Salmeterol is a β2 agonist that is used for the treatment of asthma and COPD that is poorly absorbed by the lung. Despite exhibiting robust pharmacological effects, including relaxation of smooth muscle, plasma concentrations of salmeterol are extremely low or even undetectable after inhalation. In contrast, systemic salmeterol would lead to...
changes in heart rate, QTc interval, and plasma potassium and glucose concentrations [57,58]. Long-acting β2 agonists are frequently taken with inhaled corticosteroids. However, Horvath et al. have recently shown that corticosteroids can affect expression levels of the organic cation transporters that are responsible for absorbing β2 agonists, thus dramatically affecting their bio-distribution with time [59].

Thus, direct drug delivery into the lung has proven to be advantageous for the treatment of chronic lung diseases due to the lower risk of side effects. However, such drugs must be poorly absorbed across the epithelia. More recently, groups are taking advantage of rapid pulmonary drug absorption and are investigating how to treat systemic diseases through pulmonary drug delivery since this allows for drug delivery that bypasses the stomach [60].

Conclusions

When treating pulmonary diseases such as asthma, COPD and CF, inhalation may be the best route of administration due to the rapid clinical response and the high doses of drug that can be administered to the disease site with limited off-target effects. However, a number of considerations need to be taken into account when designing new inhalation therapy formulations. Particle size, particle charge and solubility and physical characteristics of particles need to be considered as well as the ability of these particles to withstand the defense barriers presented by the lung itself. An ideal drug should also have a long half-life and minimal to no absorption across the pulmonary epithelium. Inhaled compounds must also be able to withstand degradation by ectoenzymes within the lung. A final consideration is their ability to penetrate the thick mucus often associated with respiratory diseases. Inhaled therapies may need to be administered alongside mucolytic drugs to aid penetration through mucus. Getting all of these factors to successfully align can lead to successful drug deposition within the lung followed by drug elimination without any systemic side effects.

Acknowledgement

Funded by NIH/NHLBI HL108927 and HL034322.

References


