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SYSTEMIC TREATMENT BY INHALATION OF MACROMOLECULES – PRINCIPLES, PROBLEMS, AND EXAMPLES

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Aerosol inhalation is an established tool for the treatment of pulmonary diseases since many years. In contrast, aerosol inhalation for treatment of systemic diseases is a novel therapeutic approach. Clinical use of the latter therapy for many years has been limited by the lack of accuracy and reproducibility of the administered doses and a small proportion of inhaled drug related to the dose remaining in the aerosol delivery system. Further problems were the risk of potential allergic reactions in the respiratory tract and the strong variability of drug absorption from the alveoli into the circulation. However, these problems have been solved in the last years by modern aerosol delivery systems allowing the production of an aerosol with a defined and optimized aerosol particle size combined with an optimized breathing manoeuvre and optimization of the efficacy of the nebulizers revealing a high proportion of aerosolized drug near the total amount.

Beside physical and physicochemical factors (e.g., solubility, stability within the nebulization process and electrical charge) a number of physiological parameters affect the uptake of inhaled biomolecules (e.g., peptides and proteins) after pulmonary deposition. In detail, these are inactivation (e.g., by proteolysis, oxidative inactivation by reactive oxygen species (ROS), and phagocytosis) and absorption inhibition by different absorption barriers (e.g., bronchial epithelium and alveolocapillary membrane). Pulmonary absorption can be increased by very different approaches like addition of protease inhibitors (e.g.. aprotinin) or absorption enhancers (e.g., bile acids, cyclodextrin and detergents), packing of the biomolecules into particles (e.g., liquid or solid liposomes and microspheres) or synthesis of Fc-fusion proteins. These approaches enhance the bioavailability of the inhaled substances by inhibition of proteolytic degradation and oxidative inactivation or phagocytosis (in case of antiproteases, liposomes and microspheres), solubilization of absorption inhibiting membranes (in case of detergents, bile acids, and liposomes) or increased uptake by specific cellular receptors (in case of Fc-fusion proteins). A number of these approaches are experimental and used only in animal experiments whereas others are investigated in clinical studies. However, it should be considered that absorption enhancers like the administered pharmaceuticals themselves can cause biological reactions (e.g., membrane damage by cyclodextrins and inflammatory response by hydroxymethylaminopropionic acid (HMAP)) which depend on the administered doses and the duration of the treatment and are reversible after the end of therapy.

An increasing number of studies investigated the systemic effect of inhaled high molecular weight substances (e.g., insulin, heparin, interleukin-2) and demonstrated that controlled aerosol therapy may serve as a non-invasive alternative for drug application by means of a syringe. Results of clinical studies demonstrated that the inhalation of a number of systemically active drugs is well tolerated. There are only few factors (e.g., exogen allergic alveolitis, active sarcoidosis, and active smoking) influencing alveolar drug deposition and

bioavailability of the inhaled substances. In consequence, the inhalant administration of drugs for systemic treatment will be an interesting filed in future research.

Our review summarizes the principles and underlying mechanisms for pulmonary absorption of macromolecules including the effects of absorption enhancers and gives an overview on prior research in the large field of inhalant treatment of systemic diseases.