

Delivering horseradish peroxidase as a respirable powder to the isolated, perfused, and ventilated lung of the rat: the pulmonary disposition of an inhaled model biopharmaceutical.

Selg E1, Acevedo F1, Nybom R, Blomgren B, Ryrfeldt A, Gerde P1.

1) Inhalation Sciences Sweden AB, Stockholm, Sweden.

Abstract

Our aim was to investigate the potential of the DustGun aerosol technology integrated with the isolated, perfused, and ventilated lung of the rat (IPL) to study the pulmonary disposition of an inhaled model biopharmaceutical, the 40-kDa protein horseradish peroxidase (HRP).

The DustGun aerosol technology was used to deliver respirable powder aerosols of HRP (the mass median aerodynamic diameter: 1.7 μm) as an 80-sec bolus to the IPL perfused in a single-pass mode. Lung perfusate was repeatedly sampled for 125 min after the HRP exposure. The amount of active HRP clearing with the perfusate or being retained in the lung was measured enzymatically.

The total amount of HRP deposited in the lungs was $335 \pm 100 \mu\text{g}$ and $568 \pm 47 \mu\text{g}$ for a low- and high-dose exposure, respectively. After inhalation, the initial appearance of HRP in the perfusate was rapid. However, the total amount of HRP that cleared with the perfusate remained below 0.5% of the deposited dose. The effect of opening the tight junctions between the alveolar epithelial cells on HRP absorption was studied by exposing the IPL to nebulized aerosols of either 0.02, 0.2, or 2% poly-L-Arginine (PLA) (MW 42.5 kDa) in phosphate-buffered saline (PBS) for 5 min, at 40 min after the HRP exposure. Subsequent exposure to 0.02% PLA did not affect HRP absorption. However, exposure to 0.2% PLA increased the absorption rate ninefold, and the total amount of HRP clearing with the perfusate increased to approximately 4% of the deposited dose. No further increase was obtained with 2% PLA, indicating a steep dose-response for the enhancer. It was concluded that the pulmonary absorption of HRP is quite slow, and absorption enhancers affecting tight junctions have a distinctive, yet limited efficiency. The presented inhalation technology can be very useful in studying the pulmonary absorption of biopharmaceuticals.