ABSTRACT

The purpose of this study was to investigate the activity of P-glycoprotein (P-gp) efflux pump in human airway epithelial cell models and in isolated perfused rat lung (IPL). The role of P-gp is well described at main physiological barriers; however, the exact function in the lung is not yet fully understood. Contradictory findings regarding the activity and localisation of P-gp in the Calu-3 cell line have been reported. In this study, the transport of the P-gp substrate digoxin was compared in human airway cells (Calu-3, normal human bronchial epithelial NHBE) and Caco-2 cells and the impact of P-gp on drug absorption in the IPL model was investigated. Cell layers were cultured on 1.13 cm^2 Transwell® polyester cell culture supports at an air-interface (Calu-3, NHBE cells) and under submerged conditions (Caco-2 cells) for 14 or 21 days. Integrity of the cell monolayers and the epithelial barrier of the IPL was evaluated by flux of [^{14}C] mannitol. Transport of [^{3}H] digoxin in both cell and IPL models was determined in the presence and absence of the P-gp inhibitors GF120918A and verapamil. Absorptive permeability coefficients (P_{app}) were measured in all three cell systems 0.68 - 6.02 x 10^{-6} $cm.s^{-1}$. A significantly higher (P_{app}) of digoxin in the secretory direction in Calu-3 and Caco-2 cell layers resulted in efflux ratio of 2.08 and 8.58 on day 21 in culture, respectively, which were reduced by 40.0% and 50.9%, respectively, in the presence of GF120918A. In NHBE, absorptive flux was 2.58-fold greater than the secretory flux, but flux was equivalent in the presence of GF120918A. IPL was used in single pass perfusion condition with constant inhaled air volume. The recovery of digoxin in the perfusate in 120 min after drug delivery was 41.0 ± 16.5%. The absorption profile of digoxin was not affected by the presence of inhibitor GF120918A, however, the absorption rate was significantly increased in the presence of verapamil in the perfusion solution suggesting the presence of an active efflux mechanism in the IPL model.