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Differences in drug transport across bronchial and gastrointestinal drug absorption models

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The transport of formoterol was studied in a recently developed drug absorption model of the conducting airways (16HBE14o- cells) and compared with transport in an established gastrointestinal absorption model (Caco-2 cells).

16HBE14o- cells were cultured at an air-liquid interface on collagen-coated permeable supports. The medium (DMEM: Hams F12 1:1 2 %v/v Ultroser G and 2 mM glutamine in the basolateral chamber) was replaced daily and the cells were used experimentally at day 7. Caco-2 cells were cultured according to standard methods, and the medium was replaced in both apical and basolateral chambers on alternate days. The cells were used experimentally at day 21.

A solution of formoterol containing [14C]-mannitol 2.7 μM was added to the donor chamber. Samples were removed from the receptor chamber between t=0 and t=240 min and replaced with the equivalent volume of transport medium. Formoterol concentrations were analysed by HPLC (Hewlett-Packard 1050 system, Kromasil 100 5C18 25 cm x 0.32 cm i.d. x column, mobile phase acetonitrile-phosphate buffer pH 3 (1:4), flow 0.75 $mL.min^{-1}$, and UV detection 214 nm). [14C]-mannitol and [3H]-formoterol concentrations were determined by liquid scintillation counting. Apparent permeability coefficients (Papp) were calculated using Papp = (dQ/dt).(1/(Co.A)) where dQ/dt is the transport rate, Co is the initial concentration of the solution and A is the surface area of the cells.

Several differences in the absorption characteristics of formoterol across the two models were observed. Firstly, Caco-2 cells were less permeable to the paracellular marker, mannitol, than 16HBE14o- cells (Papp = 0.31 ± 0.02 x 10^{-6} $cm.s^{-1}$ and 1.13 ± 0.25 x 10^{-6} $cm.s^{-1}$, respectively). Secondly, the transport rate of formoterol in the apical to basolateral (A-B) direction was lower in Caco-2 cells than 16HBE14o- cells, although a similar dependence of Papp on apical pH was observed in both models (Table).

	Papp (x 10^{-6} $cm.s^{-1}$)	
Apical pH	Caco-2 model [3H]-formoterol 4 μM	16HBE14o- model formoterol 0.1 mM
pH 6.0	0.36 ± 0.01	1.26 ± 0.28
pH 7.0	0.81 ± 0.02	2.28 ± 0.16
pH 7.4	1.13 ± 0.31	2.33 ± 0.32
pH 8.0	2.02 ± 0.05	3.98 ± 0.42
pH 9.0	4.00 ± 0.15	4.72 ± 0.34

Table. Apparent permeability coefficients for apical to basolateral formoterol transport across Caco-2 and 16HBE14o- drug absorption models with different apical chamber pH. Data represent mean ± s.e.m, n=3.

Thirdly, formoterol transport at pH 7.4 was approximately six-fold higher in the basolateral to apical (B-A) direction than in the A-B direction across Caco-2 cells (Papp = 7.16 ± 0.76 x 10^{-6} $cm.s^{-1}$ and 1.13 ± 0.04 x 10^{-6} $cm.s^{-1}$, respectively), but was equivalent in the A-B and B-A direction in 16HBE14o- cells (Papp = 2.33 ± 0.32 x 10^{-6} $cm.s^{-1}$ and 1.92 ± 0.15 x 10^{-6} $cm.s^{-1}$, respectively).

Assuming these differences in drug transport across bronchial and gastrointestinal absorption models to be representative of differences in drug transport *in vivo*, the value of using organ-specific drug absorption models is clear.