J. Pharm. Pharmacol. 1998, 50 (Supplement): 137

Transport of a series of D-oligopeptides across cultured 16HBE14o- and alveolar cells

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Despite the oral route being by far the most attractive for drug delivery, the gastrointestinal tract still presents many problems to the absorption of peptides and proteins. Consequently the systemic absorption of such compounds via the lung is actively being investigated. Some of the potential advantages of pulmonary delivery are that the first-pass effect is avoided and that administration is painless and relatively easy. The aim of this study was to determine the transport characteristics of a series of peptides across cultured cells derived from different parts of the bronchial tree. The [3H]-labelled peptides were synthesised in the Department of Medicine, University of Manchester, UK (He et al. 1996). The transport of the peptides across 16HBE14o- cells, derived from the human airway epithelium, and alveolar cells, isolated from the lungs of male Sprague-Dawley rats, was determined. Both cells were grown on Vitrogen-coated microporous supports. The peptides were administered in Hank's Balanced Salt Solution (HBSS) to the apical chamber and samples were taken at appropriate time points from the basolateral chamber over a four hour time period. [14C]-labelled mannitol was included in some peptide solutions to provide information on the integrity of the cell layer. The mean apparent permeability coefficient (Papp) of the peptides and mannitol was compared between the two cell models. The mean Papp for the transport of mannitol across 16HBE14o- and alveolar cells was $2.22 \pm 0.49 \times 10^{-6}$ cm s^{-1} (n=24) and $0.24 \pm 0.04 \times 10^{-6}$ cm s^{-1} (n=26), respectively. Absorption of both mannitol and peptides (Table 1) was approximately ten times slower across the alveolar cells than the bronchial cells and these results correlate with the ten-fold difference in transepithelial electrical resistances (TER's) which were in the order of 100-300 and 1000-1500 $\Omega.cm^2$ for 16HBE14o- and alveolar cells, respectively. Despite the narrow molecular weight range, there is a general trend towards decreased absorption with increasing molecular weight of the peptides across the two cell models.

Table 1. Papp of peptides across 16HBE14o- and alveolar cells (mean ± sd, n=6).

Peptide	MW	Papp ($\times 10^{-6}$ cm s^{-1})	
		16HBE14o-	Alveolar
Phe-Gly	222.2	7.29 ± 0.65	-
Phe-Val	264.3	6.04 ± 0.36	0.57 ± 0.09
Phe-Glu	290.0	4.03 ± 0.88	0.34 ± 0.04
Phe-Lys	293.4	4.31 ± 0.61	-
Phe-Ala-Val	335.4	2.53 ± 0.67	0.25 ± 0.09
Phe-Ala-Val-Ala	406.5	2.56 ± 0.19	-

A molecular weight difference of approximately 70 between the dipeptides significantly decreased Papp ($p<0.05$, student's t-test), as shown by the differences for Phe-Gly and Phe-Glu. However, there was no significant change in Papp ($p>0.05$) with increasing MW when Phe-Ala-Val was compared with Phe-Ala-Val-Ala. There were no differences ($p>0.05$) in the Papp values obtained for Phe-Glu and Phe-Lys which carry a negative and positive charge, respectively, suggesting that single charges have no influence upon the transport of dipeptides across 16HBE14o- cells. Papp values derived for the transport of the same peptides across 16HBE14o- cells in the basolateral to apical chamber were similar to those in the apical to basolateral direction, suggesting that active transport is not involved in either direction.

A clear inverse and essentially log-linear decline in oral bioavailability in rats of these peptides as a function of increasing molecular weights has been reported previously (He et al. 1996). The data derived in this study for the transport of the same peptides across both pulmonary cell models follows a similar trend.

The 16HBE14o- and alveolar cells would appear to provide suitable models for determining the transport of peptides across pulmonary derived epithelium and may aid the prediction of bioavailability for drugs delivered via the pulmonary route.

References

He, Y-L., Murby, S., Gifford, L., Collett, A., Warhurst, G., Douglas, K.T., Rowland, M. and Ayrton, J. (1996). Pharm.Res. 1673-1678