Paracellular drug transport across intestinal epithelia: influence of charge and induced water flux

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„...580, S-751 23 Uppsala , Sweden b Pharmacokinetics and Drug **Metabolism**, AstraZeneca R and D M o lndal, S-431 83 M o lndal , Sweden...creatinine and erythritol and for foscarnet using ProLogP v4.2 (**CompuDrug** NA, Rochester, NY, USA) since appropriate fragment data for..."

Abstract

The influence of drug charge and transepithelial water flux on passive paracellular drug transport was investigated in Caco-2 cell monolayers and rat ileal mucosa in vitro. Three small hydrophilic compounds with different net charges (creatinine, erythritol and foscarnet) were used as model drugs. A hypotonic glucose-rich solution was applied apically to induce epithelial absorption of water. In the Caco-2 monolayers, permeability to creatinine (positively charged) was 25-fold greater than to foscarnet (negatively charged), indicating a pronounced cation selective paracellular permeability. During apical exposure to the hypotonic glucose-rich solution, transport of all model drugs increased in both the absorptive and secretory directions. This enhanced transport coincided with a decrease in transepithelial resistance. Further, fluorescence and transmission electron microscopy indicated dilatations of the paracellular spaces but no damage to the cell membranes. These findings suggested that the enhancement in drug transport was attributable to increased paracellular tight junction permeability rather than to "solvent drag". In the ileal segments, mucosal exposure to the hypotonic glucose-rich solution had no effect on transepithelial resistance and only a marginal increase in drug transport was observed. Taken together, the modest absorption enhancement demonstrated in the in vitro models agrees with results obtained in vivo, supporting the conclusion that a more pronounced disruption of the tight junction barrier than that obtained through stimulation of epithelial absorption of water is required for efficient enhancement of paracellular intestinal drug absorption.

Author Keywords: Paracellular drug transport; Caco-2 cells; Rat ileum; Hypotonic glucose solution; Epithelial water transport; Epithelial permeability; Tight junctions; Solvent drag

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