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Characterization of valacyclovir transport mechanism across the intestinal epithelium

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Purpose : Valacyclovir is a L-valyl ester prodrug of acyclovir which is a highly effective and selective antiviral agent in the treatment of herpes virus diseases. Valacyclovir is rapidly and almost completely converted to acyclovir and increases the oral bioavailability of acyclovir three to five fold. However, the intestinal absorption mechanism of valacyclovir is not clear. If the improved absorption mechanism of valacyclovir is fully understood, it will provide a rationale of designing the amino acid ester prodrugs of polar drugs containing hydroxyl group. The main objective of our present study is to characterize the membrane transport mechanism of valacyclovir. ***Methods*** : Intestinal absorption of valacyclovir was investigated by using *in-situ* rat perfusion study and its wall permeability was estimated by modified boundary layer model. The membrane transport mechanism was also investigated through the uptake study in Caco-2 cells and in CHO-hPepT1 cells. ***Results*** : In the rat perfusion study, the wall permeability of valacyclovir was ten times higher than acyclovir and showed concentration dependency. Valacyclovir also demonstrated a D,L stereo-selectivity with L-isomer having an approximately five-fold higher permeability than D-isomer. Mixed dipeptides and cephalexin, which are transported by dipeptide carriers, strongly competed with valacyclovir for the intestinal absorption, while L-valine did not show any competition with valacyclovir. This indicated that the intestinal absorption of valacyclovir could be dipeptide carrier-mediated. In addition, the competitive uptake study in Caco-2 cells presented that dipeptides reduced the valacyclovir uptake but valine did not. Also, in IC_{50} study, valacyclovir showed strong inhibition on the ^{3}H-gly-sar uptake in CHO-hPepT1 cells over-expressing a human intestinal peptide transporter. Taken together, the result from our present study indicated that valacyclovir utilized the peptide transporter for the intestinal absorption.