Role of Monocarboxylic Acid Transporters in the Intestinal Absorption of Carboxylic Acid Drugs

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Over the past decade, tremendous amount of work has been done for the molecular characterization of transport proteins in animals and humans, which has led to a better understanding of pathophysiological roles of a number of transport proteins. Furthermore, there are increasing preclinical and clinical evidences to support the importance of transport proteins in the pharmacokinetics/toxicokinetics of a wide variety of structurally diverse drugs [1-3]. As a consequence, it is important to evaluate the contribution of a carrier-mediated mechanism to the membrane transport of drugs which may directly affect the systemic exposure, the therapeutic effectiveness and safety of drugs. Given that monocarboxylic acid transporters (MCTs) are widely distributed throughout various mammalian tissues and numerous drugs contain a carboxyl group making these compounds potential substrates for MCTs, they may have an important role in the transport of various exogenous compounds.

Many nonsteroidal anti-inflammatory drugs (NSAIDs) have a monocarboxylic acid group in their structure. Those weak organic acids are in general rapidly absorbed from the gastrointestinal tract, however, the mechanism of transport across the intestinal epithelia is still uncertain. Therefore, the present study aimed to investigate the intestinal absorption mechanism of NSAIDs, particularly the potential contribution of a MCT-mediated mechanism to the overall absorption of NSAIDs. Four structurally diverse NSAIDs such as diclofenac, diflunisal, ketoprofen and naproxen were selected and their intestinal absorption characteristics were compared in caco-2 cells as well as in rats. Diflunisal, diclofenac, ketoprofen and naproxen exhibited the strong inhibition effect on the cellular uptake of [^{14}C]-benzoic acid in caco-2 cells with IC_{50} values of 0.05 – 0.44 mM. The inhibition of naproxen and ketoprofen against the membrane transport of [^{14}C]-benzoic acid appeared to be competitive with Ki of 0.22 mM and 0.38 mM, respectively. The membrane permeability of naproxen and ketoprofen was concentration dependent, implying that the cellular uptake pathway of ketoprofen and naproxen was saturable at the high concentration. Furthermore, the cellular accumulation of ketoprofen was significantly reduced in the presence of benzoic acid and L-lactic acid, two known substrates of monocarboxylic acid transporter 1 (MCT1). These results suggest that MCT1 contributes, at least in part, to a carrier-mediated transport of NSAIDs

containing a carboxylic acid moiety across the apical membrane in caco-2 cells.

The pharmacokinetic profile of ketoprofen was also evaluated following a single PO administration of ketoprofen (1mg/kg) to rats in the absence and presence of benzoic acid or lactic acid (2 and 10 mg/kg). Pharmacokinetic profiles of ketoprofen (1 mg/kg) were significantly altered by the concurrent use of benzoic acid or lactic acid (10 mg/kg), compared to the control (given ketoprofen alone). C_{max} and AUC of ketoprofen in the presence of benzoic acid or lactic acid (10 mg/kg) were significantly ($p<0.05$) lower than those from the control group, while there was no significant change in T_{max} and terminal plasma half-life ($T_{1/2}$) of ketoprofen. Those results suggest that ketoprofen shares a common transport pathway with benzoic acid and lactic acid during the intestinal absorption in rats.

In conclusion, the present study indicated that the intestinal monocarboxylic acid transporters contributed to a carrier-mediated absorption of NSAIDs containing a monocarboxylic acid moiety.

References

[1] Ayrton A and Morgan P. Role of transport proteins in drug absorption, distribution and excretion. *Xenobiotica.* **31**:469-497 (2001).

[2] Watkins, PB. Approaches to studying the role of transporters in drug interactions in man. International Congress Series 1178 (Variability in human drug response), pp 55-67 (1999).

[3] Kim, RB. Transporters in drug disposition. *Curr Opin Drug Discov Devel.* **3**:94-101 (2000).