Membrane Permeability and Hydrolysis of Ester-Derivatives During Their Oral and Cutaneous Absorption

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Ester linkage introduction generally improves the bioavailability of therapeutic agents due to increased passive transport following oral and cutaneous administration. Carboxylesterases (CESs, EC.3.1.1.1.) that show ubiquitous expression profiles play an important role in the biotransformation of ester-containing prodrugs into their therapeautically active form in the body. The majority of CESs has been segregated into the CES1 and CES2 family and their isozymes show different substrate specificity and tissue distribution profiles.

The intestine possesses an abundance of CES2 isozyme, with the hydrolase activity of the jejunum and ileum being comparable. Rat intestine single-pass perfusion experiments have shown that CES is involved in intestinal first-pass hyrolysis. Caco-2 cells, a useful model for rapid screening of human intestinal absorption, mainly expresses CES1 isozyme but not CES2 isozyme. Because of the different substrate specificity between CES1 and CES2 enzymes, the intestinal absorption of prodrugs is difficult to predict by Caco-2 cell monolayer. Therefore, we developed a transport experimental method through Caco-2 cell monolayer under inhibition of CES, in order to evaluate the absorption of intact prodrugs.

The CES1 family isozyme presents in the skin, especially in the epidermis and dermis, with an activity is much lower than the liver but only 3-fold lower than the lung. In the transport experiment through rat skin, prodrugs were slowly transported in the hydrophilic epidermis from the stratum corneum as a reservoir for hydrophobic prodrugs and then rapidly hydrolyzed to parent drug by CES, resulted in the predominant transport of parent drug into the receptor fluid.