Drug metabolism and transport in mucus membrane

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Ester linkage introduction generally improves the bioavailability of therapeutic agents due to increase 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. Interestingly, the mucosal hydrolysis of isovaleryl-propranolol and temocapril was limited to their uptake rate at steady-state of intestinal absorption.

On the other hand, 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 easily partitioned into stratum corneum due to their hydrophobicity. Then 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.

The above findings indicated that hydrolase activity of the membrane was major rate determining factor for transport of prodrug containing ester linkage.