Synergistic Role of Drug Metabolizing Enzymes and Transporters in Regulating the Extent of Oral Absorption

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It is established that drug metabolizing enzymes and transporters act synergistically to reduce the oral bioavailability. It is possible for us to analyze the mechanism of absorption of prodrugs by considering these synergistic actions. For example, ME3229 was produced as an ester-type prodrug of ME3277, which is an antagonist against glycoprotein IIb/IIIa receptor. ME3229 is hydrolyzed in enterocytes to form ME3277, which is in turn extruded into the lumen via BCRP/ABCG2. These results suggest that we have to consider the substrate specificity of carboxylesterase and BCRP/ABCG2 in designing the prodrugs. On the other hand, it is possible that the conjugated metabolites are associated with the potent pharmacological action. One of the most famous examples may be the activation of morphine by its glucuronidation. Morphine-6-glucuronide formed in the liver may be excreted into the blood circulation via MRP3/ABCC3 located on the sinusoidal membrane of hepatocytes and exhibits its pharmacological action. Such metabolic activation is also reported for ezetimibe, which is used to reduce the plasma cholesterol levels. Ezetimibe glucuronide, rather than ezetimibe itself, is associated with the potent activity to inhibit the transport activity of NPC1L1, a cholesterol transporter located on the apical membrane of enterocytes. It is possible that the pharmacological action observed after administration of ezetimibe is also affected by the function of efflux transporters on the bile canalicular membrane of hepatocytes and/or apical membrane of enterocytes. In my presentation, I will discuss on the recent advance in these fields.