

제 목	Metabolic Activation of Ester-and Amide-Type Drugs by Carboxylesterases
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내 용	<p>Carboxylesterase is widely distributed in the tissues of vertebrates, insects, plants and mycobacteria. Among various tissues of animals and humans, the highest esterase activity with various substrates is found in the liver. Kidney has moderate carboxylesterase activity in the proximal tubules. Considerable esterase activity is also found in the small intestine epithelial cells and serum of mammals. Besides these tissues, carboxylesterase has been found in the lung, testis, adipose tissue, nasal mucosa and even in the central nervous system. Hepatic microsomal carboxylesterase catalyzes the hydrolysis of a wide variety of endogenous and exogenous compounds such as carboxylester, thioester and aromatic amide. Since carboxylesterases are important for metabolic activation of prodrugs and detoxification of xenobiotics, differences in substrate specificity and immunological properties of this enzyme are important in connection with choosing a suitable laboratory animal for the evaluation of biotransformation and toxicity of drugs. On the other hand, liver, kidney, intestine and serum were found to contain multiple forms of carboxylesterases in animal species and humans. In fact, we have purified more than fifteen isoforms of carboxylesterases from microsomes of liver, kidney and intestinal mucosa of nine animal species and humans, and characteristics of these isoforms were compared each other in terms of their physical and immunochemical properties. On the other hand, we have reported that hepatic microsomal carboxylesterases are induced by many exogenous compounds such as phenobarbital, polycyclic aromatic hydrocarbons, Aroclor 1254, aminopyrine and clofibrate. Later, we showed that some isoforms of hepatic carboxylesterase were induced by glucocorticoids such as dexamethasone and 16 α-carbonitrile, but other isoforms were rather inhibited by these compounds. These findings indicate that involvement of carboxylesterases in the metabolism and toxicity of drugs should be explained by the isoforms involved. Since 1991, we have carried out detailed research investigating the types of carboxylesterases involved in the metabolic activation of CPT-11, a derivative of camptothecin, to the active metabolite, SN-38. The results obtained strongly suggest that some isoforms of carboxylesterase of liver microsomes and intestinal mucosal membrane are exclusively involved in CPT-11 metabolism. In this symposium, the properties of carboxylesterase isoforms purified from liver, kidney and intestine of animal species and humans are outlined. In addition, metabolism of CPT-11, a novel antitumor agent, by carboxylesterases in relation to the effectiveness will also be discussed.</p>