

Prodrug Design Based on Substrate Specificity of Carboxylesterase Isozymes

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Mammalian carboxylesterase (CES) is involved in the metabolism of endogenous compounds and xenobiotics and the activation of prodrugs. In comparative studies of the hydrolase activity of liver and/or small intestine with CES isoforms expressed in V79 or Sf9 cells, it was found that hCE1 and hCE2 were responsible for the hydrolysis activity observed in the liver and small intestine, respectively.

hCE1 easily hydrolyzed substrates bearing a relatively large acyl group in comparison to an alcohol group (e.g., flurbiprofen derivatives, temocapril). In contrast, hCE2 prefers substrates with a larger alcohol groups than acyl groups such as propranolol derivatives and betamethasone valerate. Furthermore, in the chain length dependency of hydrolysis for benzoic acid derivatives, hCE1 showed reduced activity with decreasing alcohol chain length, while hCE2 showed the opposite dependency. Interestingly, it has been demonstrated that hCE1 possesses transacylation activity with hydrophobic alcohols rather than hydrophilic alcohols. This transacylation ability may be a contributing factor in determining the substrate specificity.

Fexofenadin, an anti-allergic drug, is an active metabolite of terfenadin with a lower membrane permeability than terfenadin in part due to efflux by MDR1. As predicted in the above result, fexofendin ethyl ester, a compound with large acyl group, was hardly hydrolyzed in the human small intestine and easily hydrolyzed in the liver. Interestingly, fexofenadin ethyl ester was not effluxed by MDR1. The fexofenadin ethyl ester was easily absorbed from the intestine and hydrolyzed in the liver, resulting in a markedly high plasma concentration of fexofenadin in rats.