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PREDICTION OF *IN VIVO* INTESTINAL HYDROLYSIS AND ABSORPTION OF PRODRUG FROM *IN VITRO* DATA

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ABSTRACT

Prodrug, a pharmacologically inactive derivative of an active parent drug, is useful to improve bioavalability of therapeutic agent. Prodrugs are mostly ester derivaties which are converted to parent drugs by hydrolases that widly exist in the body including intestine. Hydrolysis of prodrug in the intestinal epicelial cells let its bioavailability down due to efflux of parent drug into intestinal lumen (Fig.1). Prodrug orally absorbed as an intact prodrug results in a high bioavailability. In the present study, we tried to decide a reliable indication of intestinal hydrolysis capacity from the correlation between *in vitro* hydrolysis data and *in situ* single-pass perfusion data in rat jejunum.

All prodrugs tested in *in situ* perfusion experiment showed the high membrane permeability coefficient (Peff) which indicate 100% absorbance in human. *In situ* hydrolytic clearance (CLdeg) of prodrugs was same order of *in vitro* intrinsic clearance (CLint, deg) determined in 9000g surpernatant of rat jejunam homogenate (Isovaleryl-propranolol>> Temocapril> Ethylfexofenadine> Butyl-*p*-aminobenzoate> Ethyl-*p*-aminobenzoate> Oseltamivir). The sigmoidal correlation was obserbed between *in situ* hydrolysis rate and Log(CLint,deg). We have suggested that 100μL/min/mg S9 protein of CLint,deg is limitation of complete hydrolysis in a process of intestinal absorption. The proposed correlation is useful for the prediction of *in vivo* intestinal hydrolysis and absorption of prodrug from *in vitro* data.