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FUNCTIONAL CHARACTERIZATION OF CYP3A4.16 AND 3A4.18: CATALYTIC ACTIVITIES TOWARD MIDAZOLAM, CARBAMAZEPINE, ATORVASTATIN AND PACLITAXEL
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[Purpose] Human CYP3A4*16 (T185S) and *18 (L293P) are major defective alleles in Japanese. To assess their substrate-dependent functional alterations, recombinant wild-type and the two variant proteins were co-expressed with human NADPH-P450 reductase in Sf21 insect cells using a baculovirus-insect cell system.  [Methods] Midazolam, carbamazepine, atorvastatin and paclitaxel were used as substrates. Kinetic profiles toward four substrates were analyzed under the condition where linear ranges of the incubation times and P450 concentrations for the metabolites formation were obtained for each substrate. K_{int}, V_{max}, and CL_{int}(V_{max}/K_{int}) for all substrates were compared among the wild-type (CYP3A4.1), CYP3A4.16 and CYP3A4.18.  [Results and Discussion] CYP3A4.16 exhibited significantly higher K_{int} values (137 - 445%) for all substrates and significantly lower V_{max} (53%) for midazolam 1'-hydroxylation than those in CYP3A4.1. As results, CL_{int} values for all substrates were significantly decreased by 60 - 83%. In CYP3A4.18, K_{int} values were unchanged (82 - 104%) for all substrates, and V_{max} values for midazolam 1'- and 4-hydroxylation and paclitaxel 3'-p-hydroxylation were significantly decreased by 29 - 56%. CL_{int} values for midazolam 1'-hydroxylation and paclitaxel 3'-p-hydroxylation were significantly lower (59% and 47%, respectively) than those in CYP3A4.1. For carbamazepine 10,11-epoxidation, K_{int}, V_{max} and CL_{int} values of CYP3A4.18 were identical with CYP3A4.1. [Conclusions] CYP3A4.16 and CYP3A4.18 show the substrate-dependent altered kinetics compared with CYP3A4.1.

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SPECIES DIFFERENCE IN HEPATIC AND INTESTINAL METABOLIC ACTIVITY OF P450 SUBSTRATES
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[Purpose] Although extensive information on species differences is necessary to predict the pharmacokinetics in humans, there are not a lot of data sets on hepatic and intestinal metabolic activity in animals. We reported that metabolic activity of CYP3A in both intestine and liver of monkeys correlated well with that of humans1). In the present study, the hepatic and intestinal metabolic activities of animals and humans were investigated to elucidate the relationship between the intrinsic clearances (CLint's) of animals and humans using 22 substrates of human CYP1A, 2C and 2D.

[Methods] Metabolic stabilities of these 22 compounds in pooled liver and intestinal microsomes from SD rats, beagle dogs, cynomolgus monkeys and humans were measured to obtain CLint's.

[Results and Discussion] The hepatic CLint's of CYP1A and 2C substrates in three animal species were mostly equivalent to those in humans. On the other hand, the hepatic CLint's of CYP2D substrates in three animal species appeared to be higher but those in dogs and monkeys showed the good correlation with those in humans. The intestinal CLint's of CYP1A, 2C and 2D substrates in all the species were extremely low. Using these data, it was difficult to refer to species differences in intestinal metabolic activities of these substrates.