Animal models for predicting intestinal metabolism of drugs in humans
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Oral administration is the route that is most frequently employed for drug administration. As a main organ for the metabolism of drugs orally given, the gastrointestinal tract as well as the liver attracts attention. There are many drugs that extensively undergo the first-pass effects not only in the liver but also in the intestine, resulting in low bioavailability and insufficient efficacy as a result. Since it is important to prepare or find out drug candidates having high bioavailability, various methodologies have been proposed to evaluate the bioavailability of drugs. Following oral administration of drugs to experimental animals, simultaneously measuring portal and systemic blood concentration difference is one of techniques appropriate for the analysis of the local pharmacokinetics of drugs in the intestine and liver. i.e., analyses of intestinal absorption (1), enterohepatic circulation and intestinal metabolism of drugs. To our best knowledge, however, there has been no report assessing intestinal absorption efficacies of not a single but several drugs to evaluate their intestinal metabolism in rats and mice employing this methodology.

In the present study using double-cannulated rats and non-cannulated mice, we focused on the evaluation of first-pass metabolism of drugs as the substrates of CYP3A4/5 in the process of intestinal absorption. Each of three benzodiazepines [midazolam (MDZ), triazolam (TRZ) or alprazolam (APZ)] was orally given to rats cannulated into portal and jugular veins, and blood samples were taken at intervals. In non-cannulated mice given the same drug, blood samples were taken from portal and large abdominal veins by the usual method using plastic syringes. Pharmacokinetic data for the parent drugs and their 1’- and 4-hydroxylated metabolites were compared between the cannulated-rats and non-cannulated mice. The bioavailability was APZ>>MDZ=TRZ in rats, whereas APZ>TRZ>> MDZ in mice, and the values for MDZ were markedly different between rats and mice.

There are remarkable species differences in the gene expression, protein contents and catalytic activities of drug metabolizing-type cytochrome P450 (CYP) isoenzymes, which complicates the extrapolation into humans of data obtained in rodents in the drug development and human risk assessment. For development of better predictive models, CYP-humanized mice were produced and characterized by using genomic clones containing the complete coding and regulatory regions of genes, as transgenes. The utility of HAC mice into which a human CYP3A gene cluster was transduced will also be introduced as a promising model for the evaluation of intestinal metabolism of drugs by human CYP3A enzymes (2).

References:

Biography
Jiro Kuze, Ph.D, is a Senior Research Scientist in DMPK Dept., Taiho Drug Discovery Research Center. He acquired his Ph.D at Okayama University in 2010 in biopharmaceutical science.
He joined Research Laboratory of Taiho in 1992, serving mainly DMPK and Toxicokinetics.