30PE-05

FUNCTIONAL CHARACTERIZATION OF NOVEL CYP2Cv4 IN MACAQUES

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Macques are used frequently as an animal model during drug development because of their evolutionary closeness to humans. Despite their importance in drug metabolism, the information on macaque genes for drug-metabolizing enzymes has been largely scarce. We previously identified a number of the CYP genes from cynomolgus monkey liver including CYP2C76, which does not correspond to any human genes. Moreover, CYP2C76 is at least partly responsible for species difference in drug metabolism between macaques and humans, indicating the relevance for identification of species-specific CYP genes. To this end, we analyzed the rhesus genome sequence data, and successfully identified the CYP2C-like sequence (tentatively named CYP2Cv4). The CYP2Cv4 cDNA cloned from macaque liver by RT-PCR showed a relatively low sequence identity to human and other macaque CYP2C cDNAs. Real-time RT-PCR showed a preferential expression of CYP2Cv4 in liver among the various tissues analyzed. Moreover, CYP2Cv4 was located at the end of the CYP2C gene cluster in macaque genome, the location of which corresponded to the intergenic region in human genome, suggesting that CYP2Cv4 does not correspond to any human genes similar to CYP2C76. These results raised the possibility that CYP2Cv4 might be involved in species difference of drug metabolism between macaques and humans. Further characterization of CYP2Cv4 is in progress and the additional data will be presented at the meeting. The information provided by this study should help deeply understand drug metabolism in macaques.

30PE-06

IN VITRO SELECTIVE INHIBITION OF ROSIGLITAZONE ON DRUG METABOLISM ACTIVITIES OF HUMAN CYP ENZYMES

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Chemical inhibitors of cytochrome P450 (CYP) are useful tools for identification of CYPs involved in drug metabolism. Rosiglitazone is a chemical inhibitor of CYP2C8 and has been recommended as acceptable for in vitro experiments with this enzyme according to the FDA Draft Guidance (Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labeling, FDA, September 8, 2006). The aim of the present study was to evaluate the isoform-selectivity of rosiglitazone. The compound was tested for their inhibitory potential towards CYP2C8 (paclitaxel 6a-hydroxylation) and two CYP3A4-mediated reactions (testosterone 6β-hydroxylation and midazolam 1'-hydroxylation) in human liver microsomes at four concentrations (0, 1, 10 and 100 μmol/L). As a result, rosiglitazone inhibited CYP2C8-dependent paclitaxel 6a-hydroxylation but not CYP3A4-dependent testosterone 6β-hydroxylation consistent with previous research (Yamazaki et al., 2000). As a new finding, it also inhibited CYP3A4-dependent midazolam 1'-hydroxylation. Therefore, when rosiglitazone is used as a CYP2C8 inhibitor, possible CYP3A4 inhibition may be overlooked if the rosiglitazone concentration is not appropriate. Similar evaluation of other chemical inhibitors for their isoform selectivity is now needed. Since there are many candidate compounds metabolized by CYP3A4, the above information should help valid interpretations in CYP identification studies and be useful for choice of appropriate chemical inhibitors.