**29C09-1**

**CHANGES OF INTESTINAL AND HEPATIC CYP3A ACTIVITY AFTER ORAL ADMINISTRATION OF ENZYME INDUCER**

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**Purpose.** The intestinal and hepatic CYP3A4 can be induced *in vivo* by multiple dosing of drugs such as rifampin and carbamazepin. When CYP3A substrate is concomitantly administrated with these drugs, the therapeutic effect may unexpectedly decrease. It is important to know how CYP3A activity is periodically changed after administration of CYP3A inducer to achieve effective drug therapy. In this study, we investigate that the time-course of intestinal and hepatic CYP3A activity in rats after administration of dexamethasone (DEX), known as a specific CYP3A inducer.

**Methods.** DEX-21-monophosphate (DEXp) was used as a CYP3A inducer. Rats were treated with DEXp *(p.o. 50 mg/kg, once a day for 1, 3, 5 days)*. At 24 hrs after the last dosing of DEXp, the intestine and liver in rats were excised and each microsomes were prepared. CYP3A4 activity is evaluated by measuring hydroxylation of midazolam (MDZ). We periodically examined the change of CYP3A activity during 48 hrs after single DEXp treatment *(p.o 50 mg/kg)*. We also checked the effect of CYP3A induction by DEXp on the pharmacokinetics of MDZ *in vivo*.

**Results and discussion.** Both intestinal and hepatic CYP3A activity was increased by not only multiple but also single dosing of DEXP. However, induction level of CYP3A was not correlated with the dosing times. CYP3A activity after single DEXP administration was rapidly increased and reached to the maximum at 12hrs, then gradually returned to the base line by 36 hrs. Oral bioavailability of MDZ is much decreased by single dosing of DEXP. In summary, it was clarified that CYP3A was rapidly inducted by DEXP administration, but the extent of induction was not dependent on the dosing times.

**29C09-2**

**MOLECULAR MECHANISM OF HUMAN CYP2A6 INDUCTION VIA PXR AND PGC1α**

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CYP2A6 plays important roles in the metabolism of nicotine and some clinically used drugs. Large interindividual variability exists in enzymatic activity and protein level of CYP2A6 in human liver. A part of this variability might be caused by an inducible property, but the molecular mechanism of CYP2A6 induction is unclear. Rifampicin, phenobarbital, and CITCO, which are known to be activators of pregnane X receptor (PXR) and constitutive androstane receptor (CAR), induced CYP2A6 mRNA in human hepatocytes. We identified three distal DR4-like elements at -6698, -5476, and -4618 in the CYP2A6 gene, to which PXR/RXRα and CAR/RXRα could bind. In luciferase assays, overexpression of PXR or CAR could not activate the transcriptional activity of CYP2A6 promoter constructs (-6754 to -1) in HepG2. Interestingly, co-transfection of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) as well as PXR significantly enhanced the transcriptional activity of the CYP2A6 construct (3.9 fold of control). By the deletion of a possible suppresser region (-4533 to -185), the effects of PXR/PGC1α on the transcriptional activity were increased (6.9 fold of control). Deletion or mutation analyses revealed that two DR4-like elements at -5476 and -4618 are essential for transactivation by PXR/PGC1α. CHIP assay revealed that PXR and PGC1α bind to CYP2A6 chromatin. In conclusion, we found that CYP2A6 is induced via PXR and PGC1α through the DR4-like element at the distal response region. This is the first study to demonstrate the molecular mechanism of the induction of CYP2A6.