01D10-2

TUBULAR EXPRESSION OF TRANSPORTERS AND SECRETION OF CATIONIC DRUGS IN 5/6 NEPHRECTOMIZED FEMALE RATS
Kumiko Nishihara, Lin Ji, Satohiro Masuda, Toshiya Katsura and Ken-ichi Inui
Department of Pharmacy, Kyoto University Hospital, Sakyo-ku, Kyoto 606-8507, Japan.

In male rats, tubular secretion of cimetidine and expression of rat (r) OCT2/Sle22a2 protein were markedly decreased in the rats after 5/6 nephrectomy (Nx), an animal model of chronic renal failure. Because of the gender difference in rOCT2 expression, we expect that the effect on the tubular transporters by Nx may be different in female rats. In this study, we examined the renal handling of cimetidine and the expression of organic ion transporters in male and female rats after Nx. Renal handling of cimetidine was examined by in vivo experiments. The expression levels of organic ion transporters in the kidneys were determined by Western blotting. Tubular secretion of cimetidine and the rOCT2 protein expression in female rats was about 50% and 25% compared to male rats, respectively. The tubular secretion of cimetidine was also markedly decreased in female rats after Nx. In contrast to the male rats, the protein expression of rOCT2 was not changed, and administration of testosterone after Nx did not recover the renal tubular secretion of cimetidine in female rats. However, the mRNA level of rMATE1, which was newly identified as an apical H+/organic cation antiporter, was significantly decreased in female remnant kidney. In summary, urinary excretion of cationic drugs was also reduced under chronic renal failure in female rats. In female rats, some molecular mechanism(s) should be lain in addition to the decrease of renal rOCT2 expression due to the lowered plasma level of testosterone.

01D10-3

SUPPRESSION OF DRUG-INDUCED LIVER INJURY IN RATS FED A HIGH-FAT AND HIGH-SUCROSE DIET BY DIETARY INULIN IS ASSOCIATED WITH THE REDUCTION IN HEPATIC CYTOCHROME P450 AND HEPATOCYTE NUCLEAR FACTOR 4α EXPRESSION
Makoto Osabe1,2, Junko Sugatani1,2, Tadashi Wada3, Kouichi Yoshinari1,2, Tadanobu Takahashi1, Akira Ikari1 and Masao Miwa1,2
1Department of Pharmaco-Biochemistry, School of Pharmaceutical Sciences, University of Shizuoka, 2 21st Century Center of Excellence Program, 52-1 Yada, Suruga-ku, Shizuoka City, Shizuoka 422-8526, 3 Fuji Nihon Seito Corporation, 1-4-10 Shimizu-seikai, Shimizu-ku, Shizuoka City, Shizuoka 424-8737, Japan

The intake of a high-fat and high-sucrose diet (HF) for a long period of 8 weeks produced marked accumulation of hepatic and serum triacylglycerol in rats, leading to hypertriglyceremia and hepatic steatosis but not hepatic necroinflammatory lesions. There was no significant influence in the baseline levels of hepatic CYP2B, CYP2C and CYP3A proteins, but levels of CYP2E1 and CYP4A proteins were reduced. The administration of phenobarbital (PB) to HF-fed rats more promptly caused liver injury leading to cell necrosis and inflammation, compared to the standard diet (SD)-fed rats, and was associated with changes in PB-inducible P450 expression or via the CAR-mediated pathway associated with hepatic lipid accumulation. Supplementing inulin to the HF diet ameliorated PB-induced liver injury, associated with a decline in lipid accumulation and PB-induced expression of CYP2B and CYP3A. Furthermore, no significant difference in the expression of nuclear receptors, CAR, PXR and RXR proteins between the HF and HF+I groups was found in the hepatic nucleus, but the expression of NHF4α protein was significantly reduced in the HF+I group. The altered expression of CYP2B and CYP3A may be related by a reduction in nuclear expression of HNF4α. These results indicate that nutritional status led to altered hepatic metabolism of drugs and endogenous substances.