Effect of high-fat and high-sucrose diet on expression of drug-metabolizing enzymes and pharmacodynamics

Makoto Osabe

Department of Clinical Pharmaceutical Sciences, Graduate School of Pharmaceutical Sciences

Liver drug-metabolizing enzymes play a central role in the metabolism and elimination of therapeutic drugs and environmental contaminants. Information on the activities and expression of drug-metabolizing enzymes is essential for the development of customized medical treatments. The expression of drug-metabolizing enzymes in the body is affected by genetic factors and also by nongenetic factors such as environmental factors. In this study, we investigated the effect of a high-fat and high-sucrose (HF1) diet or a high-fat (HF2) diet on the expression of drug-metabolizing enzymes and pharmacodynamics.

Rats that consumed the HF1 or HF2 diet developed hepatic steatosis. The alteration in nutritional status affected hepatic cytochrome P450 and UDP-glucuronosyltransferase (UGT) levels. Messenger RNA and protein levels of UGT1A1 and UGT1A6 in the liver but not the jejunum were increased in male rats fed the HF1 diet. These protein levels did not increase in HF2-fed male rats or HF1-fed female rats. In contrast, the CYP1A2 protein level was decreased in the HF1 but not HF2 diet group, whereas CYP2E1 and CYP4A protein levels were elevated in the HF2 but not HF1 diet group. Consumption of the HF1 diet affected the in vivo metabolism of acetaminophen (APAP), the area under the APAP-glucuronide plasma concentration-time curve was elevated 2.1-fold in male rats but not female rats. In liver cell nuclei of male rats but not female rats, constitutive androstane receptor (CAR) and peroxisome proliferator-activated receptor α (PPAR α) protein levels were significantly enhanced by intake of the HF1 diet. Additionally, administration of the PPARα agonist clofibrate to male rats up-regulated UGT1A1 and UGT1A6 and down-regulated CYP1A2 in the liver. Taken together, these results indicate that nutritional status may genderspecifically influence the expression and activation of CAR and PPARα in liver cell nuclei, and this effect appears to be associated with alterations in UGT1A1 and UGT1A6 expression.