ALTERED DRUG METABOLIZING ACTIVITY OF HEPATIC CYP3A SUBFAMILY IN RATS WITH ACUTE RENAL FAILURE
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Purpose Acute renal failure (ARF) alters the pharmacokinetics of various therapeutic compounds, including not only the compounds undergoing the renal elimination but also those undergoing the hepatic. To clarify the mechanisms causing an altered pharmacokinetics of hepatically metabolized compounds, the effects of ARF on the hepatic drug metabolism were examined using the rat liver microsomes. The hepatic expression profiles of the drug metabolizing enzymes were also evaluated in normal and ARF rats, focusing on the CYP3A subfamily.

Methods ARF was experimentally induced by an intramuscular injection of 50% glycerol. The liver microsomes were prepared from normal and ARF rats with ultracentrifugation method. The NADPH-dependent drug elimination rate was determined in the conventional incubation study. Midazolam, nifedipine, and rifabutin were selected as the compounds subjected to the hepatic metabolism mediated by CYP3A1, 3A2, and 3A9, respectively. The hepatic expression of CYP3A2 and CYP3A9 was detected by Western blotting to be densitometrically quantified.

Results and Discussion In the incubation study, the metabolic rates of midazolam and nifedipine were reduced, while their affinity to the drug metabolizing enzyme increased in ARF rats. On the other hand, the rifabutin metabolic rate in ARF rats increased without any changes in the affinity. It was additionally revealed that the hepatic expression of CYP3A2 decreased, while that of CYP3A9 increased in ARF rats. These findings seem to be consistent with the observed alternations of the hepatic metabolism of midazolam, nifedipine, and rifabutin in ARF rats.

Conclusions The altered hepatic expression of the CYP3A subfamily is responsible for the altered pharmacokinetics of the hepatically metabolized compounds. The extent of the alteration varies among the CYP3A subfamily enzymes.

STIMULATORY EFFECT OF BILIARY NPC2 ON ABCG5/G8-MEDIATED CHOLESTEROL SECRETION
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Purpose Niemann-Pick C2 (NPC2) is one of biliary proteins secreted from hepatocytes, although physiological function of biliary NPC2 has not been clarified yet. In this study, considering a cholesterol binding activity of NPC2, we investigated the effect of secreted NPC2 on the biliary cholesterol secretion, which is controlled by cholesterol transporters such as ATP-binding cassette G5 and G8 (ABCG5/G8) and Niemann-Pick C1-like 1 (NPC1L1).

Method Hepatic NPC2 knockdown mice and overexpressing mice were constructed by adenovirus-mediated gene transfer system and biliary lipids in these mice were quantified. In addition, the effects of secreted NPC2 on the activities of cholesterol transporters were examined by in vitro analysis using ABCG5/G8 or NPC1L1 overexpressing cells.

Results and Discussion Analyses with NPC2 knockdown mice and overexpressing mice revealed that NPC2 positively regulates biliary cholesterol secretion. To reveal the molecular mechanism of this regulation, we performed in vitro studies and demonstrated that secreted NPC2 stimulates ABCG5/G8-mediated cholesterol efflux, but does not affect NPC1L1-mediated cholesterol uptake. Consistent with this observation, in ABCG5/G8-deficient mice, no significant changes in the biliary secretion of cholesterol were observed with hepatic NPC2 overexpression.

Conclusions These findings suggest that NPC2 functions as a positive regulator of biliary cholesterol secretion by stimulating ABCG5/G8-mediated cholesterol efflux. Since biliary cholesterol secretion is one of key factors involved in maintaining the whole-body cholesterol balance, this novel function of NPC2 may contribute to regulate cholesterol homeostasis.