IN Volvement of Multispecific Transporting System for Organic Cations in Mitochondria in the Mitochondrial Toxicity Caused by Phenformin

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[Purpose] Biguanides are a class of drugs widely used for the treatment of hyperglycemia in patients with type2 diabetes mellitus. However, lactic acidosis is a severe adverse effect of biguanides. Metformin reduces oxygen consumption and glucose production at least partly by the inhibition of mitochondrial respiratory complex I. However, excessive inhibition may cause lactic acidosis. Recently, it was reported that organic cation transporter 1 mediates the hepatocellular uptake of biguanides and may enhance their mitochondrial toxicity. In the present study, we focused on the uptake of organic cations into mitochondria in relation to the phenformin-induced mitochondrial toxicity.

[Methods] Isolated mitochondria and submitochondrial particles (SMPs) were prepared from the liver of male Sprague-Dawley rats (6-7 wks). Uptake of [14C]-tetraethylammonium (TEA) in mitochondria was examined in the absence or presence of other organic cations. Mitochondrial respiration complex I activity was determined by the oxygen consumption in isolated mitochondria or the NADH reduction by SMPs energized with glutamate/malate.

[Results and Discussion] Concentration-dependent uptake of [14C]TEA was observed and it was inhibited by various organic cations including metformin and phenformin, suggesting the involvement of multispecific transport system(s). Phenformin inhibited mitochondrial respiration complex I both in isolated mitochondria and SMPs. TEA attenuated the respiration inhibition by phenformin in isolated mitochondria while it did not in SMPs. It suggests that TEA inhibited the mitochondrial uptake of phenformin mediated by multispecific organic cation transporting system(s) in isolated mitochondria without affecting the respiratory complex I activity.

[Conclusion] Multispecific organic cation transport system(s) may enhance the mitochondrial toxicity by phenformin.

HEPATITIS C VIRUS-Related Cirrhosis Is a Crucial Factor Affecting the Expression of Hepatic Drug Transporters

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[Purpose] Hepatic drug transporters are responsible for both the hepatic uptake and the biliary excretion of drugs. Expression changes in hepatic drug transporter genes have been observed in various pathophysiological conditions. However, these studies have mainly focused on just one or two factors. In this study, we tried to identify the factors affecting the expression of hepatic drug transporters by multivariate analysis.

[Methods] The mRNA expression of 17 drug transporters was quantified using noncancerous liver tissue samples from 105 patients with liver tumors. Stepwise multiple regression analysis was carried out to evaluate the relation between the mRNA levels of hepatic drug transporters and 18 clinical variables.

[Results and Discussion] For solute carrier transporters, the mRNA level of OATP2B1 was the highest, followed by that of OCT1, OAT2, OATP1B1, OATP1B3, and MATE1. Among ATP-binding cassette transporters, MDR1, MRP2, MRP3, and MRP6 showed high levels of expression. Stepwise multiple regression analysis demonstrated the mRNA level of MRP4 to be predicted with the greatest accuracy among 17 drug transporters. Of 5 clinical variables entered into the prediction model for MRP4, hepatitis C virus (HCV) infection and liver cirrhosis were crucial factors affecting MRP4 mRNA and protein levels. Furthermore, we demonstrated that HCV-related cirrhosis influenced the mRNA levels of 8 drug transporters besides MRP4.

[Conclusions] Using multivariate analysis, we identified HCV-related cirrhosis as the factor affecting the expression of hepatic drug transporters, especially MRP4.