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HYPERGLYCEMIA ALTERATES ILEAL P-GLYCOPROTEIN VIA NOS
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[Purpose] P-glycoprotein (P-gp), one of the important drug-efflux pumps, is known to be affected by some pathological condition. Furthermore, some reports show that P-gp could be influenced by nitric oxide synthase (NOS). Here we studied alteration of intestinal P-gp expression and function under diabetic condition. In addition, we determined the participation of NOS in the mechanism.

[Methods] Type1 diabetes was induced in male ddY mice by STZ (230 mg/kg, i.p.). We analyzed ileal P-gp expression, function and NOS activity by western blotting, in situ closed loop method and colorimetry method, respectively. L-NAME (1 mg/mL), a non selective NOS inhibitor, or aminoguanidine (1mg/mL), a specific inducible NOS (iNOS) inhibitor, were added to the drinking water.

[Results and Discussion] Significant decrease of P-gp expression and function in ileum was found at 9th day after STZ-administration. Interestingly, NOS activity in ileum significantly increased at 9th day in L-NAME- or aminoguanidine-reversible manner. Furthermore, the decrease of P-gp expression was completely-suppressed by L-NAME or aminoguanidine. Our results showed P-gp expression transiently decreased at diabetic condition via NOS. From the physiological point, the functional alteration of P-gp rather than its expression seems to be more important. Whether the functional deterioration of P-gp is mediated by iNOS should be determined.

[Conclusions] Our results raise an alert that the intestinal absorption of the some oral drugs which are substrate for P-gp will be influenced under the hyperglycemic condition.

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THE ROLE OF PDZ PROTEINS IN DRUG RESISTANCE IN CARCINOMA
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Drug resistance conferred by drug efflux transporters is a significant impediment to cancer chemotherapy. ATP-binding cassette transporter family, including multidrug resistance associated protein 2 (MRP2/ABCC2) was reported to be up-regulated in carcinomas. In addition, PDZ (PSD95, Dlg, ZO-1) domain containing adaptor protein PDZK1 (NHERF3) that interacts with MRP2 is also reported to be up-regulated in human carcinomas arising in kidney, lung, colon and breast. However, functional property of this protein in carcinomas has not yet been elucidated. In the present study, we investigated the effect of co-expression of MRP2 and PDZ proteins (PDZK1, PDZK2, NHERF1) on sensitivity to anticancer agents. HEK293 cells co-transfected with MRP2 and PDZ proteins were established. For evaluate sensitivity to anticancer agents, these cell lines were exposed to several anticancer agents (cisplatin (0.1-100 uM), etoposide (0.1-100 uM) and doxorubicin (10-1000 nM) ; known as MRP2 substrates). Expression of MRP2 conferred resistance to these drugs which is consistent with results reported previously. Moreover, co-expression of MRP2 with PDZK1 or PDZK2 could show low susceptibility to etoposide compared with HEK293 cell expressing MRP2 alone. This result suggested that transport activity of MRP2 might be regulated by PDZK1 and PDZK2 in these cell lines. The detailed mechanism of acquisition of drug resistance conferred by co-expression of these proteins is under investigation.