Review

Functional Alterations of Intestinal P-Glycoprotein under Diabetic Conditions

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Received May 13, 2013; accepted June 22, 2013

The maintenance of an appropriate serum concentration of a drug is known to be important for its pharmacological effects and the prevention of unexpected adverse effects. Functional alterations of drug transporters and drug-metabolizing enzymes may influence the serum concentration of drugs through changes in its pharmacokinetics and pharmacodynamics (PK/PD). There are many drug transporters expressed in the brain, liver, kidneys, and intestine including ATP-binding cassette (ABC) transporters and solute carriers (SLCs), which contribute to the systemic distribution of various drugs. Furthermore, the expression and function of P-glycoprotein (P-gp), one of the ABC transporters, is altered by environmental factors such as lifestyle and disease. In this review, we have focused on the influence of functional alterations in the intestinal P-gp on the PK/PD of drugs administered *via* the oral route under diabetic conditions. Altered expression patterns of intestinal P-gp observed under diabetic conditions exhibit pathological stage-dependency. Furthermore, many factors, such as serum glucose, insulin, nitric oxide, and cytokines, influence expression of intestinal P-gp. Finally, to design appropriate and individually targeted pharmacotherapy, it is necessary to consider the influence of alterations in the intestinal P-gp as well as drug metabolizing enzymes under diabetic conditions based on experimental results obtained from fundamental animal research.

Key words P-glycoprotein; diabetes; small intestine; ATP binding cassette transporter

1. INTRODUCTION

Appropriate regulation of drug delivery to the body, including intestinal absorption, hepatic metabolism, renal excretion and transport into the brain across the blood–brain barrier (BBB), is important to ensure therapeutic efficacy.^{1,2)} Furthermore, maintaining appropriate serum concentrations of drugs is known to be necessary to exert their beneficial effects or to prevent unexpected adverse effects, especially for drugs with a narrow therapeutic window.³⁾ In addition, various factors, such as drug transporters, drug-metabolizing enzymes, protein binding ratios, and blood flow rate, may affect the pharmacokinetic features and pharmacological effects of drugs.⁴⁾ Because decades of research data and several review articles^{4,5)} have implicated the influence of changes in expression and/or functional activity of drug transporters on pharmacokinetics and pharmacodynamics (PK/PD) of many drugs, drug transporters may be of particular importance to achieve effective pharmacotherapy.

Drug transporters are generally classified as solute carrier (SLC) transporters or ATP-binding cassette (ABC) transporters.⁶⁾ SLC transporters including organic cation transporters and organic anion transporters carry specific substrate drugs by passive transport or co-transport.⁶⁾ In contrast, ABC transporters including P-glycoprotein (P-gp), breast cancer resistance protein, and multidrug resistance-associated protein 2 use energy from ATP hydrolysis to drive the transport of many structurally diverse drugs.⁷⁾

P-gp, the best-studied ABC transporter, is present not only in tumor cells but also in various normal tissues, such as liver, kidneys, intestine, and brain.^{4,8)} In the brain, P-gp is located on the luminal surface of brain capillary endothelial cells,

where it is an integral component of the BBB and actively pumps various substrate drugs out of the brain, thereby limiting brain access and regulating the pharmacologic effects of these substrate drugs.^{9–11)} Moreover, P-gp expressed in the liver canaliculi or renal tubules are known to play a physiological role in detoxification and/or protection of the body against toxic xenobiotics and metabolites by secreting these compounds into bile¹²⁾ or urine, respectively.^{4,6,13)} P-gp located on the apical plasma membrane of the small intestine regulates the absorption processes of various substrate drugs from the intestine to the systemic circulation by transporting them to the intestinal lumen.^{6,14)} Because P-gp plays an important role in tissues to pump out the large number of its substrates often used in the clinic including anticancer drugs, antihypertensive drugs (e.g., calcium channel blockers), antihyperlipidemic drugs (e.g., 3-hydroxy methylglutaryl CoA inhibitors) and others,^{15,16)} many researchers have investigated the influence of changes in P-gp on the pharmacological effects of its substrate drugs and possible mechanisms for inducing changes in the expression and functional activity of P-gp.^{4–6)}

Currently, most of the drugs used in clinical practice are administered *via* the oral route. Numerous reports using specific inhibitors or genetic knockouts have clearly indicated that P-gp can influence the serum concentrations of several drugs administered *via* the oral route.^{17–20)} Because intestinal P-gp acts as the first barrier for drugs administered *via* the oral route,¹⁴⁾ intestinal P-gp is likely to play a critical role in the uptake and absorption of its substrate drugs administered *via* the oral route (Fig. 1). In fact, there are some reports that the PK/PD of various drugs administered *via* the oral route were largely affected in mice lacking the P-gp gene^{21–23)} or treated with a P-gp inhibitor^{11,24)} as well as in cases of combination use with P-gp substrate drugs in animal^{25–27)} and human studies.^{28–31)}

The authors declare no conflict of interest.

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Fig. 1. Intestinal Drug Absorption and P-gp-Mediated Drug Excretion

After substrate drugs of P-gp administered *via* the oral route were diffused to the intracellular compartment of intestinal epithelial cells, they were excreted into the intestinal lumen by P-gp located on the apical membrane of intestinal epithelial cells. White arrow; drug absorption, black arrow; drug elimination.

Furthermore, it is well known that the expression and/or drug efflux activity of P-gp can be modulated not only by inherited factors, such as genetic polymorphisms,^{32–36} but also environmental factors, such as dietary habits,^{37–39} medicines^{25,40–42} or several diseases^{43–47} including epilepsy, seizure and diabetes. Among these diseases, the prevalence of diabetes—classified as either type 1, characterized by dysfunction of pancreatic β cells, leading to insulin depletion, or type 2, characterized by dysfunction of the insulin receptor (insulin resistance) or by impairment in insulin secretion—was estimated to be as much as 9.2–9.8% of the adult population worldwide in 2011, and this prevalence is expected to increase over the next 20 years.^{48,49} More interestingly, there are various reports focusing on changes in the expression and functional activity of P-gp in the brain, liver, kidney and intestine, especially under diabetic conditions.^{50–54}

The large number of anti-diabetic drugs, such as glibenclamide,^{55–57} rosiglitazone,⁵⁸ metformin^{58,59} and repaglinide,^{60–62} as well as several dipeptidyl peptidase-4 (DPP-4) inhibitors including sitagliptin,^{63,64} vildagliptin, saxagliptin^{65,66} and linagliptin⁶⁷ have been found to be substrates for P-gp. Because of this trend, it has been proposed that P-gp expressed in various tissues may have the potential to affect the distribution, metabolism, and excretion processes of the anti-diabetic drugs noted above under diabetic conditions. In contrast, because anti-diabetic drugs are often used in the oral form in the clinic, it might be necessary to consider changes in the expression of intestinal P-gp, which has a critical role in the absorption process of its substrate drugs administered *via* the oral route. However, there have been only a few reports that have focused on changes in intestinal P-gp and/or the influence of these changes on the PK/PD of anti-diabetic

drugs under diabetic conditions. Therefore, we focused on the activity of intestinal P-gp under diabetic conditions.⁶⁸ In the clinical literature, there have been no clinical reports evaluating the possibility that influences of alterations in the expression and functional activity of intestinal P-gp under diabetic conditions can alter the PK/PD of substrate drugs for P-gp used for patients with diabetes. Therefore, it seems important to monitor for possible alterations in the PK/PD of substrate drugs for P-gp when using oral medications for patients with diabetes in the clinic.

In this review, we focused on the mechanism of changes in the expression and/or function of P-gp in particular in the intestine under diabetic conditions as well as possible influence of diabetic conditions on the PK/PD of certain drugs, which are predicted to be frequently prescribed for patients with diabetes.

2. FACTORS RESPONSIBLE FOR INTESTINAL P-GLYCOPROTEIN EXPRESSION CHANGES UNDER DIABETIC CONDITIONS

Although the detailed mechanism by which the expression and functional activity of intestinal P-gp are changed under diabetic conditions remains unclear, we discuss several factors associated with these phenomena in this section.

2.1. Glucose Alterations in intestinal P-gp under diabetic conditions may involve a direct mechanism mediated by hyperglycemia (*i.e.*, higher concentration of blood glucose). Some *in vitro* studies have revealed that high-glucose stress decreases P-gp expression, leading to higher intracellular drug accumulation in MCF-7 cells derived from human breast cancer cells.⁶⁹

Several studies have shown that in a type 1 diabetic model induced by streptozotocin (STZ) treatment, which destroys pancreatic β cells, expression and drug-efflux activity of intestinal P-gp were significantly decreased.^{51,68,70,71} Our previous study has demonstrated that decreases in the expression of intestinal P-gp were observed in the early phase of the diabetic condition (9th day after STZ administration) accompanied by an increase in blood glucose levels.⁶⁸ In contrast, P-gp recovered to the control levels on the 15th day after STZ administration,⁷⁰ indicating alterations of P-gp may depend on the stage of diabetes. Additionally, these changes were observed in every part of the small intestine (*i.e.*, duodenum, jejunum, and ileum) at least in the case of STZ-induced type-1 diabetes model mice. These findings suggest that the expression levels of intestinal P-gp are unstable and these alterations are likely to occur early in the diabetic condition, and it is proposed that clinicians may need to pay attention to possible alterations in the PK/PD of substrate drugs for P-gp *via* intestinal P-gp when using these drugs in patients with diabetes. However, Zhang *et al.*⁷¹ have reported that the protein expression of intestinal P-gp is continuously decreased if hyperglycemic conditions last for a prolonged period (approximately 1–2 months after STZ administration), which means “chronic stage.” Furthermore, they have demonstrated that mRNA levels of P-gp are also decreased simultaneously.⁷¹ These series of findings clearly demonstrates that alterations in the expression of intestinal P-gp in an STZ-induced type 1 animal model have pathological stage-dependency. The alteration in the expression of intestinal P-gp is thought to be induced before or during the development of the hyperglycemic condition rather than a result of chronic hyperglycemia. Because an altered expression of intestinal P-gp is predicted to influence the PK/PD of its substrate drugs after oral administration, it seems to be necessary to investigate the possible diabetic stage-dependent changes in the PK/PD of substrate drugs for P-gp in each individual patient.

Furthermore, because type 2 diabetic patients exhibit complex pathological characteristics including obesity and hypertension as well as hyperglycemia, it is difficult to attribute the cause of various changes observed within the context of type 2 diabetes to hyperglycemia alone. Although a growing body of evidence is accumulating that focuses on type 2 diabetes using various animal models, a few studies have investigated the expression of intestinal P-gp under type 2 diabetic conditions. Recently, we have investigated the changes in the expression of intestinal P-gp under type 2 diabetic condition by using a monosodium glutamate (MSG)-induced hyperglycemic obese mouse in which hyperglycemia is also associated with obesity and hyperlipidemia.⁷² In this report, we have found that the levels of P-gp expressed in duodenum and jejunum but not in ileum is significantly increased as blood glucose levels are increased in mice of a type 2 diabetes, suggesting the site specificity of alteration in the P-gp expressions under diabetic conditions.⁷² On the other hands, the expression of intestinal P-gp was slightly decreased in obese rat model induced by feeding high fat diet for 8 weeks.⁷³ Considering above conflicting findings together, an increase in the intestinal P-gp expression observed in our experiments using MSG-induced hyperglycemic obese mice might not be due to just obese-induced results. In addition, Wu *et al.* have shown that P-gp expression in the capillaries of brain

striatum is increased in New Zealand obese male mice, a type 2 diabetic animal model, exhibiting hyperglycemia, hyperinsulinemia and genetic obesity.⁷⁴ In contrast, Nowicki *et al.* have reported that in a type 2 diabetic mice model induced by the combination use of a high fat diet with STZ, the expression levels of hepatic and renal P-gp are almost unchanged.⁷⁵ Therefore, the altered expressions of P-gp have been observed in some type 2 diabetic models, whereas there is only one report exhibiting an alteration in the “intestinal” P-gp by using the MSG model.⁷²

Although the following reports were performed at conditions of low glucose, “glucose depletion” has been reported to cause resistance to doxorubicin, an anticancer drug, in MCF-7 cells, indicating that a low glucose condition induces an increase in the expression and/or functional activity of P-gp.⁷⁶ Furthermore, Ledoux *et al.* have reported that glucose deprivation enhances the expression of P-gp in hepatoma cells by activating transcriptional processes of the P-gp gene through a stress response of the endoplasmic reticulum involving reactive oxygen species.⁷⁷ Collectively, these reports suggest that glucose almost certainly regulates the expression of P-gp. In Caco-2 cells derived from human colon cancer cells, it has been reported that P-gp expression is increased by glucose depletion.⁷⁸ In this phenomenon, cAMP-dependent protein kinase (PKA) that can be downregulated under high glucose stress is thought to be involved. In fact, inhibition of PKA activity, which may allow the accumulation of cAMP, has been found to be a factor in decreased expression of P-gp in MCF-7 cells.⁷⁹ Other findings have shown that treatment with glucose strongly induces cAMP hyperaccumulation due to feedback inhibition of PKA activity.⁸⁰ In contrast, although reported in hepatocytes, cAMP/PKA activity stimulates the apical surface-directed trafficking of P-gp where it can actively pump out drugs, indicating the involvement of cAMP/PKA signaling in promoting post-translational modification of P-gp.⁸¹ The apparent discrepancies in terms of which effects cAMP/PKA contributes to the expression or functional activity of P-gp might be attributable to cell type-specific differences. Collectively, although it would be highly controversial and might be difficult to make a definite conclusion, these findings led us to hypothesize that high glucose is likely to be involved in the decreased P-gp expression under diabetic conditions through a cAMP-dependent mechanism.

Taken together, these findings highlight the influence of glucose concentration on P-gp function and indicate that changes in the pattern of the protein expression and drug-efflux activity of intestinal P-gp may vary according to duration of hyperglycemia, the pathogenetic mechanism, and associated diseases other than diabetes in each individual patient. Therefore, monitoring the alterations in the expression and functional activity of intestinal P-gp under these pathological conditions may become a useful tool for patients to achieve effective pharmacotherapy.

2.2. Cytokines The serum levels of some inflammatory cytokines, such as tumor necrosis factor- α (TNF- α),⁸² interferon- γ (IFN- γ),⁸³ and interleukin-6 (IL-6),⁸⁴ have been reported to be up-regulated under several pathological conditions such as diabetes, inflammatory bowel diseases and renal failure. These pro-inflammatory cytokines are known to activate some transcriptional factors including nuclear factor κ -B (NF- κ B)^{85–88} and activator protein-1 (AP-1)⁸⁹ that are medi-

ated by specific cytokine receptors, leading to alterations in the expression levels of P-gp. For example, Belliard *et al.* have reported that treatment with TNF- α significantly decreases the expression and functional activity of P-gp in Caco-2 cells.⁸²⁾ To complicate matter, it has also been shown that exposure of rat brain capillary endothelial cells to TNF- α for a short-term duration rapidly decreases transport activity of P-gp, whereas long-term exposure increases the expression and transport activity of P-gp through TNF receptor 1.⁸⁵⁾ Long-term exposure to TNF- α induces the release of endothelin (ET), which in turn ET binds to ET_A and/or ET_B receptors, leading to activation of nitric oxide synthase (NOS), protein kinase C (PKC), and other transcriptional factors such as NF- κ B.⁸⁵⁾ In fact, these mechanisms are supported by the following observations that P-gp expression levels in hepatocytes were increased *via* activation of PKC and NF- κ B in a study using a diabetic rat model.⁵⁰⁾ Moreover, IFN- γ significantly increased the expression of P-gp *via* the activation of NF- κ B, although this was observed in an *in vitro* model of inflammatory bowel disease.⁸³⁾ Collectively, inflammatory cytokines may be involved in the altered expression of intestinal P-gp by changing the transcriptional process *via* specific transcriptional factors under diabetic conditions similar to that observed in inflammatory disease.

2.3. Inducible Nitric Oxide Synthase (iNOS) iNOS is one of the factors that influences the expression of P-gp under diabetic conditions, possibly by modulating the expression of pregnane X receptor, which is one of the key regulators for P-gp in the transcriptional process.⁹⁰⁾ Furthermore, iNOS is also known to be upregulated by stimulation with inflammatory cytokines and high-glucose stress.⁹¹⁾ iNOS participates not only in the development of hyperglycemia but also in complicating diseases associated with hyperglycemia.⁹²⁾ Our previous report that focused on changes in the expression of intestinal P-gp has shown increased activity of intestinal iNOS in an STZ-induced diabetic mouse model.⁶⁸⁾ In addition, decreases in the expression of intestinal P-gp caused by diabetes were suppressed by treatment with either a nonselective NOS inhibitor or an iNOS-specific inhibitor.⁶⁸⁾ In contrast, to our knowledge, there have been no reports indicating the involvement of other types of NOS (*i.e.*, endothelial NOS and neuronal NOS) in alterations of P-gp under diabetic conditions. Collectively, these findings suggest participation of iNOS *via* NO in the mechanism by which expression of intestinal P-gp was decreased in the STZ-induced diabetic mouse model.

Although the exact mechanism by which the expression of intestinal P-gp is decreased *via* NO remains unknown, the possible involvement of enhanced ubiquitin-proteasome system for the degradation of P-gp as a post-translational process⁹³⁾ has been elucidated in our recent finding.⁹⁴⁾ It is, therefore, likely that not only transcriptional regulation but also the degradation system for P-gp would be modulated by NO under diabetic conditions. In contrast, in an MSG-induced obesity-related hyperglycemic (type 2 diabetic) mouse model, intestinal NOS activity was not affected.⁷²⁾ Thus, we have concluded that there is minimal participation of NO in the altered expression of intestinal P-gp in the type 2 diabetic mouse model. These contrasting results raises the possibility that participation of NO in the mechanism by which altered expression of P-gp is induced by diabetes varies according to the pathological condition of each individual, and that the

activation of NOS is not merely due to hyperglycemia. The magnitude of changes in the expression of cytokines that induce NOS is likely to be different and dependent on the type of diabetes.

2.4. Insulin Insulin, one of the major regulators of blood glucose levels, has also been found to affect the expression and function of P-gp.^{95–97)} In fact, some *in vitro* studies have demonstrated that treatment with insulin upregulates the expression of P-gp in hepatocytes and brain microvascular endothelial cells by activating NF- κ B through Raf-1 kinase, a signaling molecule upstream of NF- κ B,^{95–97)} both of which are located downstream of the insulin receptor.^{95,98–100)} Although there are only a few *in vivo* studies, we and others have shown that the expression levels of intestinal P-gp are significantly decreased in the STZ-induced diabetic mouse model lacking insulin.^{68,71,101)} Furthermore, Zhang *et al.* have reported that decreased mRNA and protein expression levels of intestinal P-gp under diabetic conditions (at approximately 1–2 months after STZ administration) are reversed by treatment with insulin.⁷¹⁾ At this time, however, it is still under investigation whether “insulin itself” or “improvement in diabetes with the use of insulin” restored the decreased expression of intestinal P-gp induced by diabetes. Therefore, in any case, insulin is likely to participate in the alteration of expression and functional activity of P-gp. Further investigation is needed to describe in more detail the possible involvement of insulin in the alteration of intestinal P-gp.

3. RELATIONSHIPS BETWEEN P-GLYCOPROTEIN AND ANTI-DIABETIC DRUGS AND DRUGS FOR OBESITY-RELATED DISEASES

There are various types of therapeutic drugs used in clinical practice to improve glucose homeostasis *via* different modes of action. Insulin secretagogues, such as sulfonylureas (*e.g.*, glibenclamide and glimepiride)^{102,103)} and glinides (*e.g.*, repaglinide and nateglinide)¹⁰⁴⁾ stimulate secretion of insulin; biguanides (*e.g.*, metformin) promote utilization of glucose and decrease production of glucose in hepatocytes,¹⁰⁵⁾ and thiazolidinediones (*e.g.*, rosiglitazone) improve insulin resistance by enhancing the activity of insulin on glucose and lipid metabolism.¹⁰⁶⁾ These drugs from different categories are often prescribed concurrently as combined therapy.^{107–111)} Some of these compounds have been found to be substrate drugs for P-gp, such as glibenclamide,^{55–57)} rosiglitazone,⁵⁸⁾ metformin^{58,59)} and repaglinide.^{60–62)} Therefore, it is easy to predict that the combined use of these compounds in patients with diabetes may affect their PK/PD after oral administration *via* alterations in intestinal P-gp activity. Although there are still no reports that the combined use of anti-diabetic drugs alters the PK/PD of each other under diabetic conditions *via* P-gp, there have been, in fact, some reports that inhibition or competition of intestinal P-gp may affect the PK/PD of co-administered anti-diabetic drugs. Lilja *et al.* have demonstrated in a human study that drug–drug interactions is occurred when both glibenclamide and clarithromycin, a potent inhibitor of P-gp activity, are given *via* the oral route, resulting in increases of the area under plasma concentration–time curve (*AUC*) and the peak plasma concentration (*C*_{max}) of glibenclamide.⁵⁷⁾ Furthermore, Kajosaari *et al.* determined in a human study that co-administration of cyclosporine A, an

inhibitor of P-gp activity, with repaglinide increased the *AUC* and $C_{\max}$ of repaglinide after oral administration.⁶¹⁾ Similarly, Li *et al.* have also shown in an animal study that pretreatment with efonidipine, a calcium channel blocker that is also a substrate drug for P-gp, significantly increased the *AUC* and $C_{\max}$ of repaglinide after oral administration of repaglinide in a dose-dependent manner, presumably by inhibiting the drug efflux activity of intestinal P-gp.⁶⁰⁾

Recently, DPP-4 inhibitors have shown their ability to improve blood glucose control in type 2 diabetic patients.^{112,113)} These new oral agents raise much interest for the management of blood glucose levels in patients with diabetes, and their clinical use is expected to rapidly increase.^{112–114)} Therefore, it is important to consider the influence of changes in the expression and function of intestinal P-gp on PK/PD of DPP-4 inhibitors. In fact, because sitagliptin,^{63,64)} vildagliptin,^{65,66)} saxagliptin^{65,66)} and linagliptin⁶⁷⁾ have been found to be substrates for P-gp, the PK/PD of some DPP-4 inhibitors administered *via* the oral route are likely to be altered under diabetic conditions in which the expression and/or function of intestinal P-gp may be decreased. So far, however, there have been no reports indicating the PK/PD of any DPP-4 inhibitors administered *via* the oral route is altered under diabetic conditions. As indicated here, several drugs among the oral anti-diabetic drugs are recognized as substrates for P-gp. Consequently, there may be significant risk of altering the PK/PD of oral anti-diabetic drugs and/or developing adverse events (e.g., hypoglycemia) when used in conjunction with a number of these drugs.

Although numerous sets of different diagnostic criteria have been proposed for metabolic syndrome, insulin resistance, hyperglycemia, hypertension, dyslipidemia, and central obesity are generally agreed to be the five key features.¹¹⁵⁾ It is well known that diabetes is frequently associated with other metabolic syndromes, such as hypertension and/or hyperlipidemia.¹¹⁵⁾ Hence, frequently, multiple medicines used for metabolic syndrome are concurrently prescribed to diabetic patients as pharmaceutical therapy.¹¹⁶⁾ Because several anti-hypertensive^{60,117,118)} and anti-hyperlipidemic^{119,120)} drugs have been found to be substrates for P-gp, it appears that the PK/PD of these drugs may be changed under diabetic conditions and/or when used in conjunction with anti-diabetic drugs. Therefore, it is also important to predict and/or manage both the changes in PK/PD of anti-hypertensive or anti-hyperlipidemic drugs and possible drug–drug interactions within the context of complicated metabolic changes that are likely to occur during the diabetic state. Finally, as previously described, the expression of intestinal P-gp may be decreased in patients with diabetes. Therefore, when using anti-diabetic drugs that are substrates for P-gp in therapeutic treatment for patients with diabetes, it is likely that the PK/PD of these drugs administered *via* the oral route may also be altered. Collectively, to achieve the therapeutic effects of these drugs used to keep blood glucose levels stable, it may be necessary to consider and/or monitor for changes in the PK/PD of oral anti-diabetic drugs through altered expression and/or function of intestinal P-gp in patients with diabetes.

4. INFLUENCE OF INTESTINAL P-GLYCOPROTEIN EXPRESSION CHANGES UNDER DIABETIC CONDITIONS ON THE PHARMACOLOGICAL EFFECTS OF SUBSTRATE DRUGS

As described above, diabetic conditions can alter the expression and function of intestinal P-gp. In this section, we discuss the influence of altered expression and function of intestinal P-gp under diabetic conditions on the PK/PD of substrate drugs for P-gp administered *via* the oral route that are used to treat diabetes-related diseases in conjunction with anti-diabetic drugs. Because many patients with diabetes frequently develop not only other metabolic syndromes¹¹⁵⁾ but also cancer,^{121–123)} attention is focused on the relationship between diabetes and cancer. Therefore, we introduce the effect of diabetic conditions on the PK/PD of substrate drugs for P-gp those are often prescribed for diabetic patients with cancer.

Many anti-cancer drugs (e.g., paclitaxel, vincristine, or etoposide) have been identified as substrates for P-gp.¹⁵⁾ As mentioned above, it is easily predicted that many patients with diabetes frequently develop cancer^{121–123)} and that anti-diabetic drugs, which are substrates for P-gp after oral administration, may cause alterations in the PK/PD of anti-cancer drugs in patients. Among the anti-cancer drugs, e.g., paclitaxel, which has been used widely against various types of cancer, is known to be a substrate for P-gp.^{124,125)} Lee *et al.* have demonstrated in the STZ-induced diabetic rat model that the *AUC* and $C_{\max}$ of paclitaxel are significantly increased after oral but not intravenous administration in which the mRNA expression levels of intestinal P-gp are decreased.¹²⁶⁾ They concluded that an increased absorption of paclitaxel under diabetic conditions may be attributed to decreased expression and drug efflux activity of intestinal P-gp. As observed in paclitaxel, diabetic conditions have a risk of affecting the PK of certain anti-cancer drugs that exhibit high affinities for P-gp after oral administration depending on the expression and function of intestinal P-gp.

Not only anti-cancer drugs but also analgesic drugs (including opioids such as morphine, oxycodone, or fentanyl) are frequently used in palliative care for cancer patients. Zong and Pollack have demonstrated that morphine is well known to be a substrate drug for P-gp and that morphine analgesia was enhanced in P-gp-deficient mice.¹⁷⁾ Furthermore, the World Health Organization recommends the oral administration of opioid analgesics for cancer patients to treat cancer-related pain caused by the initial stage of treatment.¹²⁷⁾ Because of this trend, it is important to consider the influence of changes in the expression and functional activity of intestinal P-gp under diabetic conditions on the PK/PD of morphine administered *via* the oral route. Our previous study has shown that expression and functional activity of intestinal P-gp are significantly decreased on the 9th day after STZ administration.⁶⁸⁾ Simultaneously, the analgesia of morphine administered *via* the oral route was enhanced and associated with an increase in serum concentration and brain content of this drug. In contrast, these changes were not observed when morphine was administered subcutaneously or intravenously, suggesting that an increase in the absorption of morphine from intestine was caused by a decrease in the expression and function of intestinal P-gp.¹²⁸⁾ Thus, it is possible that an enhancement of

morphine analgesia administered *via* the oral route under diabetic conditions was due to decreased expression and function of intestinal P-gp, leading to increased absorption of morphine from the intestine. Because not only morphine but also fentanyl,^{129,130} oxycodone¹³¹ and the majority of other opioids¹³² are recognized as substrate drugs for P-gp, it may be useful for effective palliative care to predict the possible alterations in the pharmacological effects of opioids when used in cancer patients with diabetes.

5. CONCLUSION

In this review, we have focused on alterations of intestinal P-gp under diabetic conditions. It became clear that several pathological conditions including diabetes markedly influence the expression and/or functional activity of P-gp in a wide range of tissues. Furthermore, the alteration pattern of P-gp may differ dependent on each tissue.

Importantly, in the intestine, even under the same pathological condition, changes in the expression pattern of P-gp could differ according to the pathological stage. It might be necessary to consider the pathological stage-dependent changes in the PK/PD of substrate drugs for P-gp administered *via* the oral route in the clinical setting. Nevertheless, there have been no clinical reports to challenge and/or investigate the above described problems. The reason why may be that almost everyone have not focused on the alteration of P-gp expression in patients with diabetes as a cause of issue that PK/PD of P-gp substrate drugs are different from usual in above patients. Another possibility is that changes in the P-gp expressions are transiently-induced followed by returned to baseline levels after initiation of diabetes as shown by us. Therefore, there is insufficient information about the features of PK/PD after oral administration of substrate drugs for P-gp. Although it may be difficult to apply the same logic or results obtained from animal experiments to humans, we propose that alterations of intestinal P-gp observed in animal studies cannot be ignored and may have already occurred in the clinic when patients with diabetes are administered substrate drugs for P-gp in an oral form.

In summary, to design appropriate or individually targeted pharmacotherapy, it is necessary to consider the influence of changes in the expression and function of P-gp in the intestine under diabetic conditions.

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