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Mini-Review

Drug Exsorption from Blood into the Gastrointestinal Tract

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Drugs are exsorbed from the blood across the gastrointestinal membranes by passive or active processes. In the case of a passive transport mechanism, the exsorption of drugs depends on the concentration gradients between the serosal and mucosal sides. The extent of secretion (exsorption) is determined by numerous factors such as extent of binding to serum proteins, distribution volume, lipophilicity, pKa and molecular size of drugs, and the blood flow rate in the gut. Specific transport systems such as P-glycoprotein (P-gp), organic cation and organic anion transporters are found to be involved in active intestinal secretion of drugs. Intestinal secretory transport systems reduce the extent of drug absorption sometimes resulting in low oral bioavailability. It is, therefore, important to know whether poor drug absorption is due to the involvement of specialized secretory transport systems. Modulation of intestinal secretory transport can be a means to enhance absorption of drugs with low oral bioavailability if exsorption of drugs is based on active secretion pathways that are open for control from the "outside."

KEY WORDS: intestinal secretion; exsorption; active transport; P-glycoprotein; intestinal lumen.

INTRODUCTION

There have been several reports on the transport of intravenously administered drugs into the intestinal lumen (1-6). In the past, excretion of drugs into the gastrointestinal (G.I.) tract had been thought to occur mainly via the biliary route and/or via the intestinal membrane route; the latter being considered to be a route of minor importance. The latter process may be termed exsorption which is defined as transport from the blood into the G.I. lumen. The exsorption of drugs was considered to be relatively small, because under experimental conditions the absorption process masked the reverse phenomenon.

However, several more recent studies point out that exsorption into the G.I. tract may be an important route for the elimination of certain drugs (1,6-8). The presence of specific transporters for the secretory transport of drugs from the serosal to mucosal sides has been demonstrated (Table 1). For example, one of the secretory transporters is P-glycoprotein (P-gp) which functions as an efflux transport pump for a variety of anticancer drugs and exists on the brush-border membrane of the intestinal mucosa (9). It has been noted that the intestinal P-gp is involved in exsorption of drugs from the blood into the intestinal lumen, thereby influencing drug absorption (3-5,10,11). The present review is aimed at discussing the mechanisms of exsorption of drugs from the blood across the intestinal membrane in light of recently obtained insights.

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EXSORPTION OF DRUGS FROM THE BLOOD INTO THE G.I. LUMEN

Passive Exsorption Mechanism

Most drugs are exsorbed into the G.I. lumen because of concentration gradients between the blood and G.I. lumen by passive diffusion if the drug concentrations in the blood are higher than those in the G.I. lumen. Therefore, the higher the serum concentrations of the drugs, the more exsorption from the blood into the G.I. lumen can be expected (12). The driving force for the exsorption process of drugs from the blood across the G.I. membrane appears to be similar to the driving force for the absorption process and depends on numerous factors such as the extent of binding to serum proteins, distribution volume, lipophilicity, pKa and molecular size of drugs, and blood flow rate in the gut.

The extent of binding of drugs to serum proteins is an important factor in the transport process since only unbound, free drugs can permeate through the capillary walls to the G.I. tract. Accordingly, the degree of exsorption of drugs such as phenytoin, furosemide, and aprindine which are highly bound to the plasma protein is small (Fig. 1). For example, since phenytoin is highly bound to the plasma protein, the fraction of phenytoin exsorbed into the intestinal lumen was small, being approximately 1% of the dose 2 h after intravenous administration of 10 mg/kg to rats (12). However, the extent of exsorption was increased in a dose-dependent manner from 1.1% (for 10 mg/kg) to 2.5% (for 50 mg/kg). Such a dose-dependent change in the exsorption is considered to be due to the saturation in serum protein binding of phenytoin. In addition, it is well known that the displacement of a drug from its plasma protein binding sites by other highly plasma-protein bound drugs causes a significant increase in the tissue distribution of

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Table 1. Studies on Secretion of Drugs to the G.I. Tract

Compounds	Experimental methods	Related secretory transport system	Ref. No.
ciprofloxacin	*in vitro* (Caco-2 cells)	carrier-mediated transport	47
cefazolin	*in vitro* (diffusion cell; rat)	organic anion transport	4
		organic cation transport	4
celiprolol	*in vivo* (rat)	carrier-mediated transport	37
	in vitro (Caco-2 cells)	carrier-mediated transport (P-gp)	37, 38
chlorpromazine	*in vitro* (diffusion cell; rat)	P-gp	10
cyclosporin A	*in vitro* (Caco-2 cells)	P-gp	31
daunorubicin	*in vitro* (brush border membrane vesicles; rat)	P-gp	9
digoxin	*in vitro* (everted gut sac; rat)	P-gp	5
	in situ (intestinal perfusion; rat)	P-gp	5
	in vitro (Caco-2 cells)	P-gp	25
etoposide	*in vitro* (everted gut sac; rat)	P-gp	3
	in situ (intestinal perfusion; rat)	P-gP	3
furosemide	*in situ* (intestinal perfusion; rat)		22
guanidine	*in-vitro* (brush border membrane vesicles; rabbit)	carrier-mediated transport	35
imipramine	*in situ* (intestinal perfusion; rat)		Aimori *et al.*
norfloxacin	*in vitro* (Caco-2 cells)	carrier-mediated transport	47
paclitaxel	*in vivo* (mouse)	P-gp	50
pafenolol	*in vivo* (rat)		1
phenol red	*in vitro* (diffusion cell; rat)	organic anion transport	4
		organic cation transport	4
phenytoin	*in situ* (intestinal perfusion; rat)		12
propantheline	*in vitro* (diffusion cell; rat)	P-gp	10
quinidine	*in situ* (intestinal perfusion; rat)		21
ranitidine	*in situ* (intestinal perfusion; rat)		2
rifabutin	*in vivo* (rat)		6
talinolol	*in vivo* (human)		8
verapamil	*in vitro* (diffusion cell; rat)	P-gp	10
vinblastine	*in vitro* (Caco-2 cells)	P-gp	11, 32
	in vitro (HCT-8 and/or T84 cells)	P-gp	29, 33

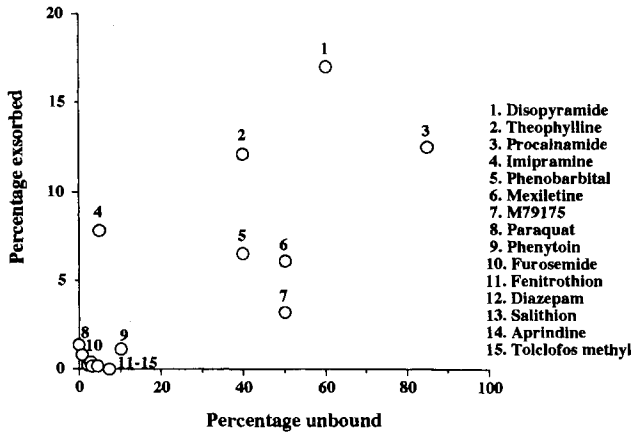

Fig. 1. The relation between fractions exsorbed and fractions of various compounds that are serum-unbound. The percentages exsorbed are the values obtained by an *in-situ* single pass perfusion technique under an identical experimental protocol by the authors (Arimori *et al.* 1985-1996). A 5-10 mg/kg dose of each compound was administered intravenously to rats. The percentages serum-unbound are the values obtained from the literature.

the drug. Imamura *et al.* (13) reported that the displacement of carbutamide from its plasma protein binding sites by salicylic acid resulted in enhanced *in situ* intestinal exsorption in rabbits. Thus, the extent of protein binding of drugs is an important factor affecting the exsorption pattern.

Exsorption from the blood into the lumen is influenced by the molecular size of the permeant in the same manner as observed with absorption. Loehry *et al.* (14) investigated the permeability by measuring the intestinal clearance of water-soluble molecules (urea, creatinine, fructose, vitamin B_{12}, inulin, and polyvinylpyrrolidone over a molecular size range of 60–33,000. They found that smaller molecules were exsorbed into the intestinal lumen at a much higher rate than larger ones.

Exsorption of hydrophilic substances, which are considered to permeate exclusively via the paracellular route, is enhanced by permeation promoters. For instance, inulin, a macromolecular, water-soluble, and hydrophilic compound is expected to permeate exclusively through a water-filled channel, the paracellular route. The exsorption of inulin from the blood into the lumen was indeed increased by promotors such as caprate, laurate, and mixed micelles (15).

There are several reports indicating that a solvent drag effect is involved in the absorption and/or exsorption process of drugs (16–18). Kitazawa *et al.* (16) reported that absorption of sulfanilamide, sulfisoxazole, and metoclopramide was increased with increasing transmucosal fluid movement from

the lumen to the blood and decreased when the movement of water was reversed. They revealed that the extent of exsorption of sulfanilamide was increased with an increase in tonicity of the perfusate, inducing an enhanced transmucosal fluid movement from the blood to the lumen. Thus, the solvent drag is considered to play a role in the intestinal absorption and/or exsorption of drugs. Porter and Baker (19) reported that 24.8% of the initial dose of intravenously administered phenobarbital was cleared during a 5-h perfusion of the G.I. tract with hypertonic electrolyte solutions containing mannitol while only 3.13% was cleared in control dogs. Young and Lee (20) also reported that a copious diarrhea induced by giving large volumes of hypertonic electrolyte solution as well as peritoneal dialysis resulted in a significant decrease in blood urea nitrogen and ameliorated the clinical symptoms of uremia in patients with renal failure. Accordingly, the effect of solvent drag could be useful for removing toxic substances from the G.I. tract in poisoned patients or patients with renal failure.

Exsorption of lipid soluble drugs from the blood across the intestinal membrane can be influenced by the "unstirred" water layer. The flux across this "unstirred" water layer is inversely proportional to the thickness of this layer. Huang (21) showed that the intestinal clearance of the two lipophilic compounds, quinidine and thiopental, was decreased by addition of pectin which increases the thickness of the "unstirred" water layer adjacent to the intestinal membrane.

There is some information on exsorption of drugs from the blood into the G.I. tract under diseased conditions. A change in other pathways of elimination such as renal or liver failure can influence the extent of exsorption. Since the total body clearance of a drug is the sum of the clearance through the renal and non-renal routes (e.g., biliary and intestinal excretion and metabolism), the decreased clearance in diseased states such as renal failure and hepatic cirrhosis results in a reduction of total body clearance. When in the diseased state, serum concentrations of the drug are higher and last longer than under normal conditions, therefore, a greater extent of exsorption can be expected.

Furosemide is partly eliminated by the renal route (mainly via tubular secretion) as an unchanged drug and partly by nonrenal routes. The exsorption rate of furosemide was increased in rats with acute renal failure compared with the rate in normal rats (22). The increased exsorption of furosemide can be explained by the delayed elimination from serum and by the decreased binding of the drug to serum protein in rats with acute renal failure. In addition, in the case of drugs which are significantly metabolized in the liver and excreted into the bile, exsorption will be increased in hepatic failure. The clearance of theophylline is decreased by hepatic cirrhosis and congestive heart failure. The delayed clearance of theophylline can cause an increased extent of exsorption. We confirmed that the exsorption of theophylline was enhanced in rats (13.4% of the dose in 2 h) with hepatic cirrhosis induced by carbon tetrachloride compared with that in normal rats (8.75% of the dose in 2 h) (23). On the other hand, the fraction of theophylline excreted into the bile was very small and there was little difference between hepatic cirrhosis rats (0.35%) and normal rats (0.33%). This suggests that exsorption across the intestinal membrane plays an important role in hepatic failure as a transfer route for a drug that is normally metabolized in the liver.

Active Exsorption Mechanism

Although passive diffusion is generally an important mechanism of exsorption for most compounds, some are subject to specialized transport mechanisms which are much more effective than diffusion. The intestinal epithelium has specialized transport systems that can secrete drugs in a serosal-to-mucosal direction, and these can function as a barrier to absorption. In the 1970s, it was demonstrated that exsorption of cardiac glycosides, quaternary ammonium ions, and organic acids from the blood side to the luminal side is performed by a certain active secretory mechanism, which was not fully understood. Recent studies suggested that specific transporters including P-gp are involved in the active secretion of drugs in the intestine (4,24–26).

P-gp mediated active secretion of drugs into the intestine has been studied extensively in many laboratories. P-gp is the multidrug transporter which mediates the active transmembrane transport of a variety of anticancer agents and causes multidrug resistance (MDR). This protein functions as an ATP-dependent efflux transport pump for a variety of drugs and causes a decrease in the intracellular concentrations and the selective toxicity of these drugs. Besides in tumor cells, P-gp is also expressed in various organs such as the kidney, liver, brain, and G.I. tract (27). Therefore, it sometimes plays an important role in the pharmacokinetics of substrate drugs, i.e., in their absorption, distribution, and elimination (28). Intestinal P-gp is involved in the active secretion of drugs such as anticancer drugs (3,11,29), organic cations (10,26), cardiac glycosides (5,25), and peptides (24,30,31) from the serosal (basolateral) to the mucosal (apical) membrane; they consequently cause low oral bioavailability (3,4). Specific secretory transport systems for drugs (including P-gp) which have been described recently are discussed below.

Anticancer Drugs

The intestinal P-gp localized in the brush-border membrane exsorbs anticancer drugs into the intestinal lumen. Leu and Huang (3) used everted gut sacs and an *in situ* perfusion technique. They showed that etoposide exsorption was decreased and its absorption could be substantially increased when P-gp was inhibited by the substrate inhibitor (quinidine), the unhydrolyzable ATP analog (AMPPNP), or the monoclonal antibody of P-gp (C219).

Vinblastine is actively secreted from the basal to apical membrane in human intestinal epithelial Caco-2 cell monolayers (11,32) and the intestinal adenocarcinoma cell line HCT-8 (29). The direct correlation of apical P-gp expression with vinblastine net secretory flux was demonstrated by reduction of the flux from basolateral to apical membrane after treatment with the monoclonal antibody MRK16 (32). The secretory flux of vinblastine was inhibited by P-gp inhibitors such as verapamil, cyclosporine, and its analog SDZ PSC 833 (29,33).

Organic Cations

There are some specific transporters involved in the active intestinal secretion of organic cations. Saitoh and Aungst (10) indicated that verapamil, chlorpromazine, and propantheline were the substrates for P-gp-mediated secretory transport using diffusion cells with rat intestinal segments. They showed that

the ileal P-gp-mediated secretory transport of verapamil differed from that of propantheline and suggested that the rat intestine may have multiple P-gp efflux systems with distinct substrate specificities depending on the intestinal site.

Tetraethylammonium (TEA) (34) and guanidine (35) are known to be transported by an active intestinal transport mechanism. These compounds are substrates for the organic cation secretory system located on the renal brush-border membrane. It was shown that TEA was not a substrate or an inhibitor of P-gp (36). Guanidine uptake was manyfold greater in the presence of an outward-directed proton gradient than in the absence of a proton gradient in the rabbit intestinal brush-border membrane (35). This proton gradient-dependent transport mechanism for guanidine was distinct from the Na^+-H^+ exchanger, because amiloride did not inhibit guanidine uptake. On the other hand, verapamil permeation was not affected by the presence of a proton gradient and verapamil did not interact with guanidine. The presence of a carrier (guanidine-proton antiport system) for guanidine transport was suggested. This carrier system is not related to the P-gp system.

ß-blockers such as acebutolol, celiprolol, nadolol, and timolol are actively transported from the blood into the intestinal lumen (26,37). The secretion of these ß-blockers from the blood into the intestinal lumen and their resulting low oral bioavailability are considered to be partially due to the contribution of P-gp. The transport of celiprolol (37,38) and acebutolol (26) from the basolateral to the apical side was found to exceed apical-to-basal transport using human Caco-2 cell monolayers. Celiprolol exhibited a time- and temperature-dependent uptake in isolated rat small intestinal epithelial cells (37). Its secretion was inhibited by substrates for P-gp such as vinblastine, verapamil, and nifedipine and was either inhibited or stimulated by typical substrates for the renal organic cation-H^+ exchanger such as cimetidine, TEA, choline, and the anionic diuretics such as acetazolamide, chlorthalidone, and hydrochlorothiazide (38). Consequently, multiple transport systems including P-gp and organic cation transporter for the ß-blockers are considered.

Cardiac Glycosides

There is evidence for intestinal secretion of cardiac glycosides. It has already been shown that digoxin is a substrate for renal P-gp (39) and further that its transepithelial secretion is inhibited by P-gp substrates including cyclosporine as observed in normal and transfected renal LLCPK1 cells (40,41). Involvement of P-gp for digoxin transport into the intestinal lumen was also confirmed in the rat everted-sac study using P-gp inhibitors, P-gp monoclonal antibody, and P-gp inducers (5) as well as in a study with human intestinal epithelial Caco-2 cells (25). Secretion of digoxin across the epithelium requires that the cardiac glycoside enters the cytosol across the basolateral membrane, before being subject to ATP-dependent secretion at the apical membrane. Cavet *et al.* (25) proposed that digoxin secretion by the intestinal epithelium is likely to involve both diffusional uptake and Na^+-K^+ pump-mediated endocytosis, followed by active extrusion at the apical membrane. It seems likely that similar transport mechanisms operate in both intestinal and renal epithelia. Accordingly, a well-described pharmacokinetic interaction between digoxin and P-gp inhibitors such as quinidine (42,43), verapamil (43), and nifedipine (44) may be based not only on the decrease in renal clearance but also the increase in the intestinal absorption.

Peptides and Others

Small peptides and peptide-like drugs such as ß-lactam antibiotics permeate through the intestinal membrane via an active transport system coupled with proton movement (45,46). This peptide transport system contributes to their appreciable absorption in spite of their low lipophilicity. Studies on active intestinal transport systems were also performed to identify the further causes of their low oral bioavailability and to further investigate the transport mechanism of certain peptides (24,31), ß-lactam antibiotics (4), and fluoroquinolone antibacterial agents (47). These compounds are considered to be secreted in the intestine by one or more specific transport mechanisms such as organic anion and/or organic cation transport systems besides P-gp.

For example, intestinal transport in the secretory direction including P-gp-mediated transport systems, has been reported on a lipophilic peptide, cyclosporin A (31), and a hydrophilic peptide, DMP728, a cyclic peptide fibrinogen antagonist which was identified as a cyclic Arg-Gly-Asp analog with high affinity and specificity for the platelet GPIIb/IIIa receptor (24). Cyclosporin A exhibits large interindividual differences in oral bioavailability presumably due to its limited solubility, poor intestinal permeability, and first-pass metabolism during transport through the gut wall and in the liver. Another mechanism for consideration is the existence of a P-gp transmembrane pump located in the intestinal mucosa which contributes to the low oral bioavailability as observed with cyclosporin A therapy. Augustijns *et al.* (31) demonstrated that the permeability coefficient value at 0.5 μM cyclosporin A in a basolateral-to-apical direction is 10-fold higher than the value determined for the apical-to-basolateral direction using human Caco-2 monolayers. In addition, apical-to-basolateral transport rate of cyclosporin A (0.5 μM) increased 3-fold in the presence of P-gp inhibitors such as chlorpromazine and progesterone, whereas basolateral-to-apical transport decreased to less than 25% of that observed in the absence of inhibitors.

Aungst and Saitoh (24) reported that the permeation in the secretory direction of DMP 728, a cyclic peptide fibrinogen antagonist, greatly exceeded its transport in the absorptive direction using the diffusion cell of rat intestinal segments. It is not confirmed whether DMP728 is a substrate for the intestinal peptide transport system since cephradine, L-carnosine, and ampicillin, which are known substrates of the peptide absorptive transport system, and Arg-Gly and Gly-Asp had no significant effects on DMP 728 permeation. Mucosal-to-serosal permeation of DMP728 was increased by a monoclonal antibody to P-gp. Mouse IgG, a nonspecific antibody, also increased mucosal-to-serosal permeation of DMP728. Most known P-gp substrates generally have a hydrophobic nature and have a cationic function group. DMP728 is zwitterionic and very hydrophilic at neutral pH. Accordingly, the active transport systems including P-gp may be involved in DMP 728 transport.

CLINICAL SIGNIFICANCE OF DRUG EXSORPTION TO THE G.I. TRACT

The exsorption of drugs into the G.I. tract plays an important role in disposition of drugs. First, in the G.I. tract,

"normal" absorption occurs, but it is also an important site for excretion and reabsorption of drugs. Drugs are excreted via the biliary route and/or across the G.I. membrane from the blood into the G.I. lumen generally by passive diffusion and also by active transport mechanisms requiring energy. The drugs transported into the G.I. tract are partly reabsorbed from the G.I. membrane and the remaining is excreted into the feces. This enterohepatic and/or entero–entero circulation can influence drug elimination from the serum, apparently resulting in an extended half life.

These excretion routes can be seen as a means of detoxification in drug poisoning. The G.I. mucous membranes have a large surface area when including the stomach and the small and large intestines. The total absorptive and/or exsorptive area of the small intestine is about 200 m^2 in an adult human. If the G.I. mucous membrane acts as a dialysis membrane, a considerable amount of drug could enter the G.I. lumen, mostly by passive diffusion in drug overdoses. It has been demonstrated that orally-administered activated charcoal not only prevents drug absorption from the G.I. tract, but also increases the clearance of drugs that were already absorbed and are in systemic circulation (12,48). This so-called G.I. dialysis (49) is one of the hemo-purification methods in drug poisoning. The value of G.I. dialysis is determined by the extent to which excess drug and poisonous compounds are transported into the G.I. tract. Therefore, it is important to have information on the characteristics of exsorption of drugs from the blood into the G.I. tract since whole bowel irrigation is often performed as a decontamination procedure in drug poisoning. Whole bowel irrigation cannot only clean the bowel, but also enhance the clearance of the excess drugs in the blood if they are efficiently exsorbed (and not reabsorbed) into the intestinal lumen.

Second, it is also important to know whether poor absorption of a drug is due to the involvement of a secretory transport system. Intestinal secretory transport systems can reduce the apparent extent of absorption and may be an unrecognized cause of low oral bioavailability. The intestinal epithelial membrane has some specialized transport systems which can secrete drugs from the serosal site to the mucosal site and these can function as a barrier to absorption. A typical intestinal secretory transport system is P-gp, as described above. P-gp can be a factor that limits bioavailability of some hydrophobic drugs and peptides in addition to unfavorable physicochemical properties and a first-pass metabolism. The inhibition of intestinal P-gp and disruption of functional P-gp could decrease intestinal exsorption and increase the extent of absorption of drugs, resulting in increased bioavailability (3,50).

Consequently, modulation of intestinal specialized transport systems could be a means to enhance absorption of drugs with low oral bioavailability if the drugs are subject to active secretion. However, we should be aware of the potentially complex pharmacological responses caused by the compounds that increase the extent of absorption.

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