Valproic acid (VPA, Fig. 1) \(^1\), a simple, branched-chain fatty acid with a broad spectrum of anticonvulsant activity, is widely used for treatment of various forms of epilepsy (Rimmer and Richens, 1985). A major metabolic pathway of VPA is glucuronidation of the carboxylic acid. The other minor pathways are \(\beta\)-oxidation and \(\omega\)-hydroxylation at aliphatic hydrocarbon side chains (Eadie et al., 1988). Valproic acid glucuronide (VPA-Glu) metabolite is known to be excreted into urine of rat, dog, monkey, and human (Vree and Van der Kleijn, 1977; Dickinson et al., 1979).

The chemical structure of VPA differs very much from other antiepileptics, thus, VPA is often applied in combination with other anticonvulsant agents (Cloyd et al., 1985). Numerous types of drug-drug interactions between VPA and concomitantly administered drugs have been reported, e.g., reduction in the plasma concentration of VPA by phenytoin or phenobarbital due to induction of hepatic drug-metabolizing enzymes (Richens et al., 1975); enhanced VPA hepatotoxicity by phenytoin or carbamazepine due to the formation of 4-ene-VPA, a minor but toxic metabolite of VPA (Levy et al., 1990); and inhibition of plasma protein binding of VPA by salicylic acid (Fleiman et al., 1980; Yu et al., 1989) or by endogenous free fatty acid (Bowdle et al., 1982). A clinically interesting drug interaction of VPA with Carbenin [panipenem (PAPM)/betamipron, Sankyo Co., Ltd., Tokyo, Japan], a carbapenem antibiotic, has been reported recently in three patients, who showed a reduction of trough plasma level of VPA during concomitant treatment with Carbenin (Nagai et al., 1997). A similar interaction was also found during concomitant therapy with VPA and meropenem, another carbapenem antibiotic. Carbapenem antibiotics have a broad spectrum of antibacterial activity that includes moderate activity against Gram-positive bacteria, excellent activity against Gram-negative aerobics and anaerobics (Shimada and Kawahara, 1994; Fish and Singletary, 1997), and are used frequently in treating various infections. These interactions resulted in the recurrence of epileptic seizures in patients and, therefore, prohibition of the concomitant use of carbapenem antibiotics with VPA was newly added to Information on Adverse Reactions to Drugs (Ministry of Health and Welfare, Japan, 1996).

More recently, it was established that PAPM (Fig. 1), a pharmacologically active constituent of Carbenin, affects the pharmacokinetics of VPA also in cynomolgus monkey (Ministry of Health and Welfare, Japan, 1996). We previously reported that the VPA-PAPM interaction also occurred in Beagle dog and was related to the glucuronidation of VPA (Yamamura et al., 1998). The details of the interaction mechanism, however, have not yet been clarified.

In this report we examined the effect of PAPM on the hepatic excretion of VPA-Glu in rat. Additionally, we investigated whether PAPM alters VPA uptake by rat hepatocytes and plasma protein binding of VPA.
\[
\text{\text{CH}_3\text{-CH}_2\text{-H}_2\text{C}} \quad \text{CH-COOH} \quad \text{valproic acid}
\]
\[
\text{\text{CH}_3\text{-CH}_2\text{-H}_2\text{C}} \quad \text{HOOC} \quad \text{N} \quad \text{H} \quad \text{H} \quad \text{NH} \quad \text{N-C-CH}_3
\]

**panipenem**

**FIG. 1.** Chemical structures of PAPM and VPA.

Experimental Procedures

**Materials.** Male, Sprague-Dawley (SD) rats (Charles River, Ibaragi, Japan) were housed in a well ventilated room maintained at 24°C and were allowed free access to food and water. The body weight of the rats used for the experiments ranged from 200 to 350 g. Rats were fasted for 12 h before use. Sodium valproate and \(\beta\)-glucuronidase were purchased from Sigma Chemical Co. (St. Louis, MO). \(^{14}\)C-Labeled sodium valproate \((^{14}\text{C-VPA, specific activity: 55 mCi/mmol, chemical purity: 99\%})\) and \(^{3}\)H-labeled sodium valproate \((^{3}\text{H-VPA, specific activity: 15 Ci/mmol, chemical purity: 99\%})\) were obtained from American Radiolabeled Chemicals Inc. (St. Louis, MO). PAPM was synthesized in our laboratories (Miyadera et al., 1991). Silica gel plates (Art. 5715) for thin-layer chromatography (TLC) were purchased from E. Merck (Darmstadt, Germany). Other chemicals used were commercially available, reagent grade products.

**In Vivo Study.** Plasma concentration-time profile of VPA in normal SD rats, nephrectomized rats, and hepatectomized rats. The normal rats were lightly anesthetized with ether during the experiments and the femoral vein was cannulated with polyethylene tubing. Thirty minutes after starting the PAPM infusion, 1.43 mg/min/kg PAPM was administered through the femoral vein catheter. The femoral vein catheter was cannulated with polyethylene tubing. Thirty minutes after starting the PAPM infusion, 1.43 mg/min/kg PAPM was administered through the femoral vein catheter. Blood samples of about 0.3 ml each were collected from the jugular vein at scheduled intervals for a period of up to 120 min and immediately centrifuged at 12,000 rpm for 3 min to separate plasma samples. Plasma concentrations of VPA were measured by fluorescence polarization immunoassay (TDx/TdxFLx system, Abbott Laboratories, Abbott Park, IL). Nephrectomized rats were prepared by removing both kidneys after ligating both the renal vein and artery under light ether anesthesia.

**In Vitro Study.** Initial uptake of VPA into isolated rat hepatocytes. Rat hepatocytes were isolated with a slight modification of the method described by Moldeus et al. (1978). The viability of cells was assessed by the trypan blue exclusion method and cells with 90% or higher viability were used for the experiments. The initial rate of VPA uptake was measured by the method described by Schwenk (1980). The hepatocytes were suspended in Krebs-Henseleit buffer at a final cell density of 2 \(\times\) 10\(^6\) cells/ml; 0.95 ml of this solution was preincubated at 37°C for 3 min before addition of \(^3\)H-VPA (0.05 mCi/ml). At 0.5 min after addition of the substrate, 0.2-ml aliquots were removed and centrifuged immediately through a silicone oil layer into 3 M KOH to separate the cells from the incubation medium. The radioactivity of the solubilized cells in the alkaline layer was determined in a liquid scintillation spectrophotometer. VPA uptake was calculated as an amount of VPA in pmol (the radioactivity in the pellet divided by the specific activity of \(^3\)H-VPA) incorporated in 10\(^5\) cells in 30 s (pmol/10\(^5\) cells/30 s).

**Plasma unbound fraction of VPA.** Animals were sacrificed by exsanguination from the abdominal aorta under light ether anesthesia. Blood samples collected into plastic tubes containing EDTA were immediately centrifuged to separate plasma samples. To determine the free fraction of VPA, with or without PAPM or salicylate, VPA (final concentration 50, 100, or 150 \(\mu\)g/ml) and PAPM (final concentration 50 \(\mu\)g/ml) were added to plasma and, after incubation at 37°C for 15 min, centrifugal ultrafiltration of the plasma was carried out through an MPS-3 membrane (Amicon Division, W.R. Grace & Co., Beverly, MA) at 2500 rpm for 15 to 30 min. The concentration of VPA in plasma (Cp) and filtrate (Cu) was measured by fluorescence polarization immunoassay. The adsorption of VPA to MPS-3 membrane was negligible. The plasma unbound fraction was calculated as Cu/Cp.

**Hepatic tissue unbound fraction of VPA.** Animals were sacrificed by exsanguination from the abdominal aorta under light ether anesthesia. The liver was quickly isolated and homogenized with twofold volumes of 10 mM Tris-HCl (pH 7.4). Cytosol from 30% homogenate was prepared by centrifugation at 9,000 g for 20 min at 4°C followed by ultracentrifugation (105,000 g for 60 min at 4°C). To determine the free fraction of VPA (final concentration 25 \(\mu\)g/ml) in the presence of PAPM (final concentration 0, 20, or 200 \(\mu\)g/ml), VPA and PAPM were added to the cytosol and the mixture was treated in the same way as above for plasma protein binding.
β-Glucuronidase activity in the liver toward VPA-Glu. Three rats were sacrificed by exsanguination under ether anesthesia and the livers were quickly isolated and homogenized in 3-fold volumes of 20 mM potassium bicarbonate buffer (pH 6.8). This homogenate was used as the enzyme source of β-glucuronidase. Because VPA-Glu was the major metabolite in the bile after i.v. administration of [14C]-VPA to the rats above in vivo study, the bile samples were collected over a period of 2 h after administration of VPA (30 mg/kg) to three rats combined and used as VPA-Glu. To measure the concentration of VPA-Glu in the pooled bile sample, the bile was hydrolyzed under alkaline condition as follows. A 0.2-ml aliquot of the bile was added with 0.1 ml of 5 N NaOH and incubated at room temperature for 2 h. The reaction was stopped by the addition of 0.1 ml 5 N HCl and the pH of the sample was adjusted to approximately 7 with 0.2 ml 1 M potassium bicarbonate buffer (pH 7.4). Then, the sample was applied to the TDx/TDxFLx system to measure the concentration of VPA.

A 0.1-ml aliquot of the bile was added with 0.25 ml of the liver homogenate or 20 mM potassium bicarbonate buffer (pH 6.8) and the mixture was incubated at 37°C. For the time course study at 15, 30, and 60 min after starting the incubation, 0.07-ml aliquots were removed and added to 0.02 ml of 1 M citric acid to stop the reaction. The pH of the sample was adjusted to approximately 7 with 0.06 ml of 1 M potassium bicarbonate buffer (pH 7.0) and centrifuged by an Eppendorf centrifuge. The supernatant was measured for the concentration of VPA. For the inhibition by PAPM, 0.02 ml of the bile was added with 0.05 ml of the liver homogenate and 0.01 ml of PAPM (final concentration 0, 50, or 500 µg/ml). The mixture was incubated at 37°C for 1 h and treated in the same manner as above.

Pharmacokinetic Analysis. For individual rats, model-independent pharmacokinetic parameters, i.e., area under the plasma concentration-time curve (AUC(tot)), biological half-life (T1/2), and distribution volume (Vd) were calculated using WinNONLIN (Scientific Consulting, Inc., Cary, NC) software. Total body clearance of VPA (CLtot), the apparent metabolic clearance of VPA by glucuronidation (CLm(glu)), and the biliary excretion clearance of VPA-Glu (CLbile(glu)) were calculated as follows:

\[
\text{CL}_{\text{tot}} = \frac{\text{Dose}}{\text{AUC}_{\text{tot}}}
\]

\[
\text{CL}_{\text{m(glu)}} = \frac{\text{V}_{\text{bile(glu)}}}{\text{Css,plasma(vpa)}}
\]

\[
\text{CL}_{\text{bile(glu)}} = \frac{\text{V}_{\text{bile(glu)}}}{\text{Css,liver(glu)}}
\]

where Css,plasma(vpa) is the plasma concentration of VPA at steady state, and Vbile(glu) is the concentration of VPA-Glu in the liver at steady state, and Vbile(glu) is the biliary excretion rate of VPA-Glu.

Statistical Method. All results are shown as means ± S.D. Statistical differences in pharmacokinetic parameters between VPA alone and PAPM-treated groups were tested by Student’s t test. The criterion for statistical significance was p < 0.05.

Results

In Vivo Study. Effects of PAPM on plasma concentration-time profiles of VPA in normal SD rats, nephrectomized rats, and hepa-rectomized rats. The time courses of the plasma concentration of VPA, with or without PAPM treatment, in normal SD rats and in nephrectomized rats are shown in Fig. 2 and Fig. 3, respectively. VPA rapidly disappeared from plasma in both groups of rats with PAPM treatment. Significant increases in the CLm(vpa) as well as a significant reduction in the T1/2 by PAPM treatment were observed in both the normal SD rats and nephrectomized rats (Table 1). In contrast, PAPM did not affect the pharmacokinetic behavior of VPA in nephrectomized rats, which showed markedly prolonged elimination of VPA (Fig. 4 and Table 1).

Effect of PAPM on cumulative biliary excretion of metabolites after bolus injection of 14C-VPA. The thin-layer chromatogram of bile and the time profile of the plasma concentration of [14C]-VPA in bile-fistula rats are shown in Fig. 5. In bile-fistula rats, PAPM still enhanced the elimination rate of VPA. As shown in Table 2, 90% or more of the minor metabolites (BM-1 and BM-2), found at amounts not more than 2.4%, was observed between the PAPM-treated group and the control group.

Effect of PAPM on hepatobiliary excretion of VPA-Glu under steady-state condition of VPA. The result under steady-state condition of VPA is shown in Table 3. The PAPM treatment caused a decreasing tendency of Css,plasma(vpa) and an increasing tendency of Css,liver(glu), although the differences in these values were not statistically significant between PAPM-treated and control rats. CLm(vpa) and Vbile(glu) were 1.2- and 1.5-fold higher, respectively, in the PAPM-treated rats than in the control rats. CLbile(glu) was also a 1.8-fold higher in the PAPM-treated rats than in the control rats. CLbile(glu) values were nearly identical in the PAPM-treated and the control rats. In addition, the contribution of the clearance parameters other than
CL m(glu) to CL tot (CL tot minus CL m(glu)), namely the clearance due to other elimination pathways, was not affected by the PAPM treatment. Thus, the increase in CL m(glu) by the PAPM treatment was concluded to be the major reason for the increased CL tot in the PAPM-treated rats.

In Vitro Study. Effects of PAPM on initial uptake of VPA by rat hepatocytes. The initial velocity of VPA uptake by rat hepatocytes was linear over a concentration range from 1 to 200 μM and independent of temperature (Fig. 6). Addition of PAPM at 50 or 200 μM did not affect the initial uptake.

Effects of PAPM on plasma unbound fraction of VPA. As shown in Fig. 7, there was no significant difference in the plasma-unbound fractions of VPA determined in vitro at 50, 100, or 150 μg/ml between plasma containing PAPM (50 μg/ml) and the control plasma. In contrast, a clear increase in the plasma-unbound fraction of VPA (p < .001) was observed by addition of salicylic acid (final concentration 250 μg/ml), a known inhibitor of plasma protein binding of VPA.

Effect of PAPM on hepatic tissue-unbound fraction of VPA. As shown in Table 4, addition of PAPM (20 or 200 μg/ml) did not significantly affect the tissue-unbound fractions of VPA in hepatic cytosol determined in vitro at 25 μg/ml.

Effect of PAPM on hepatic β-glucuronidase activity toward VPA-Glu. The concentration of VPA-Glu in the bile, which was used as the substrate solution in this experiment, was 0.415 μmol/ml (60 μg/ml as VPA). VPA produced from VPA-Glu by the action of β-glucuronidase in 25% liver homogenate proportionally increased as a function of incubation time up to 60 min (result not shown). Therefore, the effect of PAPM on hepatic β-glucuronidase activity toward VPA-Glu was investigated after incubation for 60 min as shown in Table 5.

| Table 1 |

Pharmacokinetic parameters of VPA in normal rats, nephrectomized rats, and hepatectomized rats, with or without PAPM treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>S.D.</th>
<th>Nephrectomized</th>
<th>PAPM treatment</th>
<th>Hepatectomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VPA alone</td>
<td>PAPM treatment</td>
<td>VPA alone</td>
<td>PAPM treatment</td>
<td>VPA alone</td>
</tr>
<tr>
<td>CL tot (ml/h/kg)</td>
<td>343.3 ± 62.0*</td>
<td>605.2 ± 47.4*</td>
<td>258.8 ± 43.9</td>
<td>423.5 ± 58.7*</td>
<td>125.5 ± 39.5</td>
</tr>
<tr>
<td>T ½ (h)</td>
<td>0.44 ± 0.09</td>
<td>0.18 ± 0.01</td>
<td>0.58 ± 0.07</td>
<td>0.27 ± 0.06*</td>
<td>1.56 ± 0.46</td>
</tr>
<tr>
<td>V d (ml/kg)</td>
<td>211.6 ± 13.2</td>
<td>161.6 ± 17.4*</td>
<td>218.5 ± 51.4</td>
<td>165.5 ± 50.2</td>
<td>265.9 ± 25.3</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

* Values are the mean ± S.D.

PAPM, Panipenem; VPA, Valproic Acid; T ½, Half-life; V d, Volume of distribution.

Hepatectomized rats were prepared by ligating the hepatic artery and hepatic portal vein and VPA (30 mg/kg) was administered intravenously (see details in text).

![Fig. 4. The plasma concentration-time course of VPA in hepatectomized rats with (○, n = 3) or without (●, n = 3) PAPM treatment.](image1)

Hepatectomized rats were prepared by ligating the hepatic artery and hepatic portal vein and VPA (30 mg/kg) was administered intravenously (see details in text).

![Fig. 5. Typical chromatogram of bile after administration of 14C-VPA (A) and the plasma concentration-time course of VPA in rats with a bile duct fistula (B), with (○, n = 3) or without (●, n = 5) PAPM treatment.](image2)

Rats were prepared with a bile duct cannulated and collected bile after intravenous administration of 14C-VPA (30 mg/kg). Bile sample with ethanol was subjected to TLC with n-butanol:acetic acid:distilled water (4:1:1; see details in text).
Addition of PAPM (50 or 500 μg/ml) caused no effect on the VPA production from VPA-Glu by liver homogenate.

**Discussion**

The drug interaction between VPA and PAPM is due to the pharmacokinetic interaction, because the marked reduction of trough plasma level of VPA was recognized in every patient (Nagai et al., 1997). The mechanism of the interaction is noteworthy because the physiochemical and pharmacokinetic characteristics of VPA and PAPM are completely different.

In a series of in vivo studies, it was found that i.v. administration of PAPM significantly reduces $T_{1/2}$, but did not alter the maximum plasma concentration ($C_{max}$) of VPA after oral administration of VPA to monkey and dog (Ministry of Health and Welfare, Japan, 1996; Nouda and Perez, 1997; Yamamura et al., 1998). In the present study, a similar result was obtained in rat with a significant reduction in AUCinf and a significant increase in CLtot of VPA by PAPM coterat-

---

**TABLE 2**

Proportion and cumulative recovery of each metabolite in bile after intravenous administration of $^{14}$C-VPA at 30 mg/kg, with or without PAPM treatment

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Proportion of each metabolite in bile</th>
<th>Cumulative recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TLC %</td>
<td>% of Dose</td>
</tr>
<tr>
<td>VPA</td>
<td>2.7 ± 1.2$^a$</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>BM-2</td>
<td>3.9 ± 0.6</td>
<td>4.2 ± 2.6</td>
</tr>
<tr>
<td>VPA glucuronide</td>
<td>89.4 ± 1.5</td>
<td>38.3 ± 0.7</td>
</tr>
<tr>
<td>BM-1</td>
<td>2.9 ± 0.8</td>
<td>2.6 ± 0.6</td>
</tr>
</tbody>
</table>

$^a$ The batches of bile collected (90–120 min) were assayed.

---

**TABLE 3**

Effect of panipenem on bilary excretion of VPA-Glu in rats under steady-state conditions, with or without PAPM treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VPA alone</th>
<th>PAPM treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>.Css, plasma (vpa) (μg/ml)</td>
<td>102.1 ± 11.3$^b$</td>
<td>85.1 ± 6.6</td>
</tr>
<tr>
<td>Css, liver (glu) (μg/g liver)</td>
<td>69.0 ± 25.9</td>
<td>90.5 ± 16.8</td>
</tr>
<tr>
<td>B.E.R. (glu) (μg/min/kg)</td>
<td>174.4 ± 38.1</td>
<td>261.2 ± 33.6$^a$</td>
</tr>
<tr>
<td>CL$_{in}$ (ml/h/kg)</td>
<td>246.7 ± 20.8</td>
<td>295.5 ± 7.4$^a$</td>
</tr>
<tr>
<td>CL$_{in}$ (ml/h/kg)</td>
<td>104.7 ± 30.8</td>
<td>185.1 ± 30.0$^a$</td>
</tr>
<tr>
<td>CL$<em>{in}$–CL$</em>{in}$ (ml/h/kg)</td>
<td>142.3 ± 13.0</td>
<td>110.4 ± 37.5</td>
</tr>
<tr>
<td>CL$_{in}$ (ml/h/kg)</td>
<td>179.5 ± 112.7</td>
<td>190.9 ± 62.1</td>
</tr>
</tbody>
</table>

$^a$ Values are the mean ± S.D., n = 3.

---

**TABLE 4**

Effect of PAPM on unbound fraction of VPA in hepatic cytosol

<table>
<thead>
<tr>
<th>Panipenem added</th>
<th>VPA unbound fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>μg/ml</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>92.0 ± 2.6$^a$</td>
</tr>
<tr>
<td>20</td>
<td>93.2 ± 1.6</td>
</tr>
<tr>
<td>200</td>
<td>94.9 ± 2.0</td>
</tr>
</tbody>
</table>

$^a$ Values are the mean ± S.D., n = 3.

---

**TABLE 5**

Effect of PAPM on hydrolysis of VPA-Glu by liver β-glucuronidase

<table>
<thead>
<tr>
<th>PAPM added</th>
<th>VPA deconjugated from VPA-Glu (μmol/h/g liver)</th>
</tr>
</thead>
<tbody>
<tr>
<td>μg/ml</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3.593 ± 0.119$^a$</td>
</tr>
<tr>
<td>50</td>
<td>3.573 ± 0.239</td>
</tr>
<tr>
<td>500</td>
<td>3.793 ± 0.047</td>
</tr>
</tbody>
</table>

$^a$ Values are the mean ± S.D., n = 3.
CL_{int,H} is a hybrid parameter including uptake by the liver, metabolism, and biliary excretion of VPA and/or its metabolites. As shown in Fig. 8, the increase of CL_{int,H} can occur at steps 2, 3, 4, 5, 6, and 7. The initial uptake of VPA by hepatocytes occurred by passive diffusion consistent with the previous report (Booth et al., 1996) and was not affected by PAPM (Fig. 6). Thus, the uptake step of VPA was not considered to increase the CL_{int,H} by PAPM (Fig. 8–2). It is reported that the binding of VPA in the liver is partly ascribed to the intracellular ligandin (Yu and Shen, 1995). However, more than 90% of VPA in the hepatic cytosol was protein unbound and was not affected by the PAPM treatment in vitro (Table 4). Therefore, the displacement of hepatic-protein binding of VPA by PAPM is negligible (Fig. 8–3). The glucuronidation was confirmed to be the major pathway of VPA in rats as shown in Table 2 and Fig. 5. The β-oxidation and ω-hydroxylation of VPA (Fig. 8–4) are the minor pathways and were not considered to be important in the drug interaction with PAPM. We also observed that PAPM did not inhibit the β-glucuronidase activity toward VPA-Glu as shown in Table 5 (Fig. 8–6). The fact that the increase in CL_{m(glu)} by the PAPM treatment was the major reason for the increased CL_{m(glu)} in the PAPM-treated rats under steady-state condition means a negligible contribution of β-oxidation and ω-hydroxylation pathways in the interaction (Table 3).

This CL_{m(glu)} is a parameter including steps 5 and 7 in Fig. 8. The CL_{m(glu)} indicated the excretion process of VPA-Glu (Fig. 8–7) was not affected. It is considered that unaffected CL_{m(glu)} but increased V_{bile(glu)} is due to the increased Css,liver(glu) and thus, it is indicated that PAPM does not enhance the biliary excretion process of VPA-Glu Therefore, the site of action of PAPM to enhance the glucuronidation of VPA is consequently considered after only one step, namely, the glucuronidation step (Fig. 8–5) from this study.

It has been reported (Dickinson et al., 1979) that the biliary excretion of VPA-Glu in the rat is very high (45–55% of the administered dose) but VPA and VPA-Glu are not excreted in the feces, showing that VPA undergoes extensive enterohepatic recirculation as a consequence of biliary excretion of VPA-Glu and after deconjugation and reabsorption. Kojima et al. (1998) reported recently that the decrease in numbers of enteric bacteria that are able to deconjugate VPA-Glu by PAPM results in shutdown of the enterohepatic recirculation of VPA and is regarded as a possible mechanism for the VPA-PAPM interaction. However, the biliary excretion of VPA-Glu shows a species difference, as it has been reported that the biliary excretion of VPA-Glu in monkeys is very limited (3–7% of the administered dose; Dickinson et al., 1980). The interaction between VPA and PAPM occurred in both species. This fact indicates that the abolished deconjugation of VPA-Glu and the decreased reabsorption of VPA are very unlikely as the mechanisms for the VPA-PAPM interaction.

The biochemical mechanism of the interaction between VPA and PAPM has not been elucidated yet, but the following factors are considered as possible reasons for the increased glucuronidation of VPA: 1) enzyme induction of UDP-glucuronosyltransferase (Fig. 8–5) and 2) increased cofactor availability [UDP-glucuronic acid (UDPGA), Fig. 8–5; Rowland and Tozer, 1980].

Repeated administration of anticonvulsant drugs such as carbamazepine is well known to cause the reduction of plasma level of VPA due to enzyme induction (Richens et al., 1976), which generally takes a relatively long time, whereas the reduction of the plasma VPA level due to interaction with PAPM is immediately observed after coadministration (Nagai et al., 1997). Therefore, it is unlikely that the induction of UDP-glucuronosyltransferase explains this drug interaction.

The cofactor availability is considered to be one of the most possible mechanisms for the drug interaction between VPA and PAPM (Fig. 8–5). Because the glucuronidation is a bimolecular...
reaction between the substrate and UDPGA. UDPGA is an essential determinant for the conjugation reaction. As an example of the availability of UDPGA being rate-limiting in glucuronidation, Braun et al. (1997) have demonstrated that pretreatment by GSH-depleting agents causes the enhancement of glycogenolysis, the increase of UDP-glucose supply originating from glycogen metabolism. Arch Biochem Biophys 348:169–173.

In conclusion, the increase in CL_{tot} of VPA by PAPM is mainly due to the increased hepatic intrinsic clearance, especially the enhanced glucuronidation of VPA.

References


