Contents

1. Introduction

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) inhibit the synthesis of mevalonate, a rate-limiting step in cholesterol biosynthesis, leading to a reduction in the plasma low density lipoprotein (LDL)-cholesterol level. High plasma LDL-cholesterol is a risk factor of cardiovascular diseases and, therefore, cholesterol-lowering drugs are used to prevent them. Some randomized controlled trials have shown that statins have potent cholesterol-lowering effects and reduce the risk of cardiovascular diseases in everyday medical practice (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995; Sacks et al., 1996; Bertolini et al., 1997; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998). On the other hand, some of statins exhibit a number of adverse effects, such as myopathy or rhabdomyolysis (Staffa et al., 2002; Thompson et al., 2003). Concomitant use of other drugs sometimes increases the risk of severe myotoxicity (Pierce et al., 1990; Pogson et al., 1999). Cerivastatin causes a serious myotoxicity, which has resulted in 31 deaths in the USA (Staffa et al., 2002). Among these patients, 12 were concomitantly taking gemfibrozil, suggesting that combination therapy with these drugs might increase the risk of side effects due to a drug–drug interaction (Staffa et al., 2002). Indeed, the plasma concentration of cerivastatin was reported to be increased by

coadministration of gemfibrozil (Backman et al., 2002). Due to this severe side effect, cerivastatin was voluntarily withdrawn from the market in 2001. This review will summarize the mechanism of drug–drug interactions between statins and other drugs, using comparisons of the characteristics of statins, their physicochemical properties, elimination routes, and so on.

Mevastatin, a lead compound of the statins, is a fungal product, initially extracted from *Penicillium citrinum* (Endo et al., 1976). Lovastatin, simvastatin and pravastatin are also derivatives of fungal products (Alberts et al., 1980; Hoffman et al., 1986; Endo, 1992). Among them, lovastatin and simvastatin possess a lactone ring in their structure and are transformed into the active open acid form in the body while pravastatin is administered as the biologically active open acid form (Fig. 1). On the other hand, fluvastatin is a completely synthetic statin with a very different structure from the statins derived from fungal products (Fig. 1). Fluvastatin is a mevalonolactone derivative with a fluorophenyl-substituted indole ring (Fig. 1). Statins, which reached the market after fluvastatin, also have similar structures with fluorophenyl groups. All of the totally synthetic statins have open acid forms. Depending upon their chemical structures, they have different affinities for HMG-CoA reductase, which determines their pharmacological effects, and different pharmacokinetic properties (i.e. tissue distribution, metabolic stability, enzymes and transporters involved in their metabolism, etc.). Thus, the information on the physicochemical properties of statins is useful to understand their pharmacokinetic properties. Drugs which interact with statins depend upon the pharmacokinetic properties of each of statins.

Recently, some reports on genetic polymorphisms in drug metabolizing enzymes and transporters have been published and interindividual differences in the pharmacokinetics of statins associated with them have been reported (Kirchheiner et al., 2003; Nishizato et al., 2003; Kajinami et al., 2004a; Niemi et al., 2004; Wang et al., 2005). This review also summarizes the information on the interindividual differences in pharmacokinetics of statins associated with these genetic factors.

2. The mechanisms governing the pharmacological effect of statins

2.1. Direct mechanism on 3-hydroxy-3-methylglutaryl coenzyme A reductase

All statins currently on the market possess a HMG-like moiety (Fig. 1): simvastatin and lovastatin have a lactone ring instead of this moiety and are transformed into the

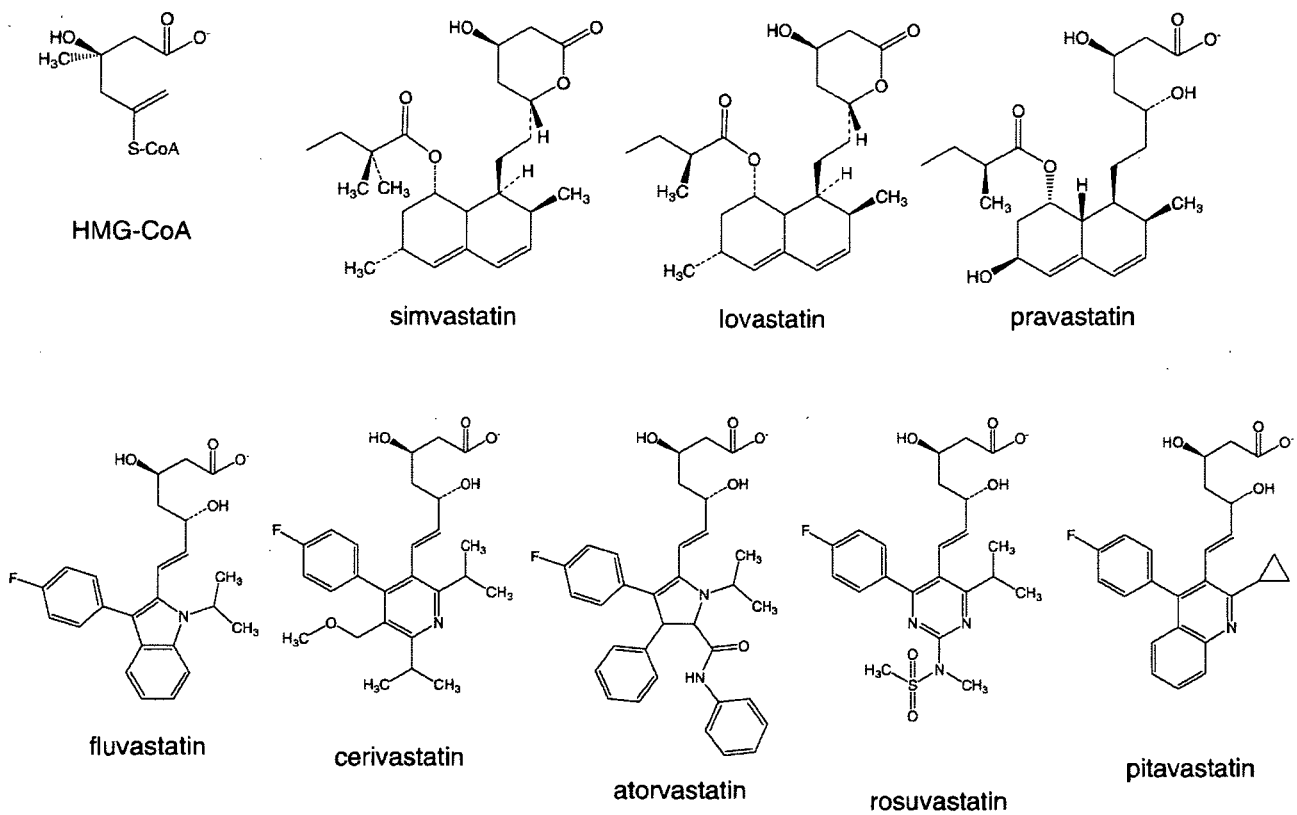

Fig. 1. Chemical structures of HMG-CoA reductase inhibitors (statins). Among statins, simvastatin, lovastatin and pravastatin are derivatives of fungal products while other newly developed statins are completely synthetic. The fungal products, simvastatin, lovastatin and pravastatin, are structurally related and they have a hydronaphthalene ring in common. Simvastatin and lovastatain are orally administered as inactive prodrugs in the lactone forms while pravastatin is given in the active open acid form. Other totally synthetic statins have different structures although they also have an open acid HMG-like moiety between the 4-fluorophenyl- and isopropyl- (or cyclopropyl-) groups. The difference in structure accounts for their different solubility in water.

biologically active form with an open acid in the body while other newer statins are administered as the open acid forms. Newer statins with HMG-moieties have a higher affinity for HMG-CoA reductase and exert more potent inhibitory effects (Istvan & Deisenhofer, 2001; McTaggart et al., 2001; Holdgate et al., 2003). Enzyme activity assay of HMG-CoA reductase substrate catalytic fragments indicates that statins, including simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin and rosuvastatin, have a high affinity for HMG-CoA reductase with inhibition constants (K_i) of 5–44 nM while the Michaelis constant (K_m) of HMG-CoA is 4 μM, suggesting that all statins are potent inhibitors of this enzyme (Istvan & Deisenhofer, 2001; McTaggart et al., 2001; Holdgate et al., 2003).

Fig. 2 shows the pathway for the biosynthesis of cholesterol. HMG-CoA reductase-mediated production of mevalonate is a rate-determining step of cholesterol biosynthesis and, thus, inhibition of this enzyme reduces the cholesterol level. A reduced serum cholesterol level leads to an upregulation of LDL-receptors by a transcriptional regulation to maintain the intracellular cholesterol by homeostasis (Brown & Goldstein, 1986; Lennernas & Fager, 1997). However, cytochrome P450 7A1 (CYP7A1, cholesterol 7α-hydroxylase), which is specific to the liver, transforms intracellular cholesterol to bile acids, leading to a reduction of cholesterol in hepatocytes, although it is taken up via upregulated LDL-receptors. Biodegradation of cholesterol in the liver results in a reduction of total cholesterol in the body. In addition, the liver plays an important role in the biosynthesis of lipoprotein and catabolism of LDL (Brown & Goldstein, 1986). About 50% or more of the total cholesterol in the body is endogenous and it is mainly synthesized in the liver (Grundy, 1978; Peters et al., 1993; Gadbut et al., 1995; Transon et al., 1996). Thus, the target organ of statins is the liver.

2.2. The mechanism governing the side effect: the involvement of statin-produced inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase

Patients taking statins sometimes suffer from a number of adverse effects (i.e. myopathy or rhabdomyolysis). Their detailed mechanism is still unknown but some hypotheses have suggested that inhibition of HMG-CoA reductase may directly cause this myotoxicity (Thompson et al., 2003).

Cholesterol is also synthesized in the extrahepatic tissues and this biosynthesis plays an important role in normal cell function and steroid hormone biosynthesis (Corsini et al., 1999). Exposure of statins to extrahepatic tissues suppresses their cell function, leading to adverse effects, with little pharmacological effect (Sirtori, 1993). The reduction in cholesterol biosynthesis in muscle cells by statins leads to a reduction in their cholesterol contents of the plasma membrane. This may cause instability of the plasma membrane and damage to the cells. However, this hypothesis conflicts with the fact that cholesterol reduction by squalene synthase inhibition does not trigger myotoxicity (Flint et al., 1997; see Fig. 2).

Inhibition of HMG-CoA reductase results in the reduced biosynthesis of farnesyl pyrophosphate, an intermediate metabolite of ubiquinone/coenzyme Q_{10} (CoQ_{10}; Fig. 2). CoQ_{10} is a steroid isoprenoid which plays an important role in the cellular energy transduction in the mitochondrial electron transport system. In addition, it is a vital electron and proton carrier and supports ATP synthesis in the mitochondrial inner membrane, and stabilizes cell membranes, preserving cellular integrity and function. Thus, a reduced CoQ_{10} level may be one of reasons causing myotoxicity. Indeed, a reduction of serum CoQ_{10} level was reported in patients of myofiber atrophy and muscular dystrophy although it was not observed in patients of myofiber predominance and lower motor unit disease (Miles et

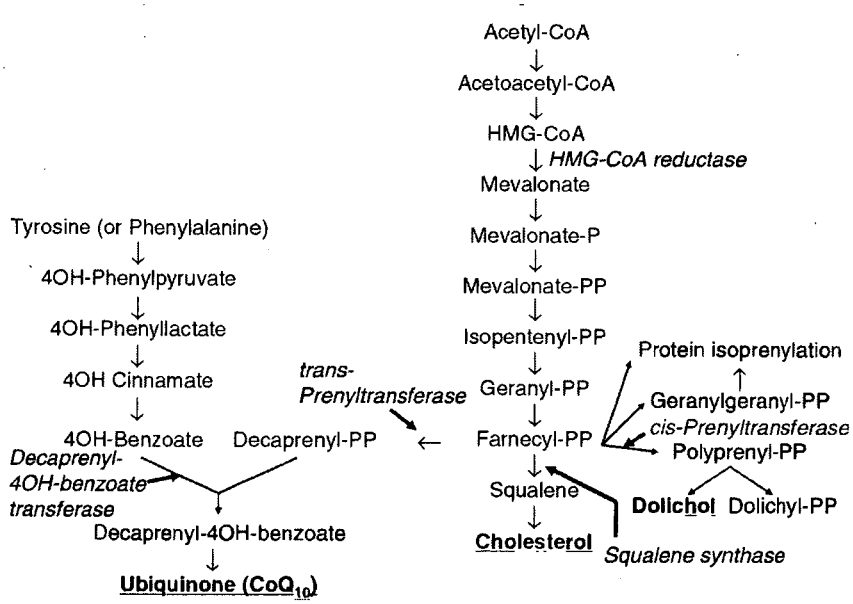

Fig. 2. Biosynthesis of cholesterol. Cholesterol is synthesized from acetyl-CoA. The synthesis of mevalonate, mediated by HMG-CoA reductase, is the rate-limiting step, which regulates the cholesterol synthesis. Farnesyl pyrophosphate is a branch point for the biosynthesis of other polyisoprenoids, dolichol and ubiquinone.

al., 2005). In addition, myopathy was reported to be associated with muscle CoQ_{10} deficiency (Lalani et al., 2005). 50% of total CoQ_{10} in the body is endogenously synthesized and, in patients taking statins, reduced serum CoQ_{10} levels have been reported (Folkers et al., 1990; Ghirlanda et al., 1993). Laakson et al. reported that CoQ_{10} in the skeletal muscle is not reduced by administration of statins while Paiva et al. showed that it is reduced in patients taking a high dose of simvastatin (Laaksonen et al., 1995, 1996; Paiva et al., 2005). Thus, some reports do not support the relationship between statin-induced myotoxicity and CoQ_{10}. However, the hypothesis that statin-induced myotoxicity is associated with reduced CoQ_{10} cannot be refuted because there are no data about the CoQ_{10} level in the skeletal muscles in patients routinely taking statins. There are other data supporting this hypothesis. In patients taking statins, the ratio of lactate to pyruvate increases, suggesting mitochondrial dysfunction (De Pinieux et al., 1996). In addition, biopsy samples from patients with statin-induced myopathy suggest mitochondrial dysfunction (i.e. increased lipid storage and ragged red muscle fibers), although the intracellular CoQ_{10} level has not been measured (Phillips et al., 2002).

On the other hand, there is a report that reduced synthesis of farnesyl pyrophosphate and geranylgeranyl pyrophosphate led to a reduction in the prenylation of small GTP-binding proteins such as Ras, Rac and Rho, which is thought to result in apoptosis of muscle cells (see Fig. 2). Pravastatin and lovastatin reduce the synthesis of these proteins in neonatal rat myocytes (Flint et al., 1997). This reduction can be reversed by the addition of farnesol and geranyl geraniol. On the other hand, myotoxocity was not observed when cholesterol was reduced by the inhibition of squalene synthase. These facts suggest that statin-associated myotoxicity is caused by farnesol and geranyl geraniol, intermediate metabolites in cholesterol synthesis, but not by cholesterol itself. Johnson et al. showed apoptosis of differentiated L-6 myoblast cells was not associated with the intracellular CoQ_9 and CoQ_{10} levels (Johnson et al., 2004). On the other hand, they showed this apoptosis was suppressed by the addition of mevalonate and geranylgeraniol, but not by the addition of farnesol (Johnson et al., 2004). Their results support the possibility of the involvement of the reduction in the protein geranylgeranylation in the myotoxicity associated with statins.

2.3. Other effects involving antiatherosclerosis

The direct mechanism of statins in preventing atherosclerosis and cardiovascular diseases by inhibition of cholesterol biosynthesis associated with the inhibition of HMG-CoA reductase is described above. However, statins also prevent cardiovascular diseases by other mechanisms (Corsini et al., 1999). As described above, mevalonic acid, the synthesis of which is inhibited by statins, is a precursor of not only cholesterol but other metabolites including isopentyl adenosine contained in transfer RNA, dolichols for the synthesis of glycoproteins and CoQ_{10} (Fig. 2). In addition, metabolites of mevalonic acid including farnesyl pyrophosphate and geranylgeranylpyrophosphate mediate the prenylation of some specific proteins (Fig. 2). Prenylated proteins are involved in a number of processes including cell signal transduction, differentiation, proliferation, myelination and cytoskeleton dynamics. Thus, statins may protect from the atherosclerosis by modulating such cell function triggered by the inhibition of protein prenylation.

The effects of statins, in addition to the inhibition of cholesterol biosynthesis, are summarized in Table 1. Statins affect arterial myocytes, macrophages and metaloproteases by these mechanisms and prevent atheroscelosis.

2.4. Association between the pharmacological effect of statins and genetic polymorphisms which affect the cholesterol level

Until now, there have been a large number of pharmacogenetic studies to examine the interindividual difference in the lipid level in the circulating blood and outcome response by statin therapy. By these studies, more than 30 genes have been investigated looking at statin responsiveness. Among them, some genes are directly related to the cholesterol biosynthesis or hypercholesterolemia while others are studied in relation to the pharmacokinetics of statins (Kajinami et al., 2004b, 2005). Table 2 summarized the candidate genes which have been investigated in pharmacogenetic studies to explore the determinants of statin therapy (Kajinami et al., 2004b, 2005). The relationship between the pharmacological and/or toxic effects of statins and genetic polymorphisms of factors which affect the cholesterol biosynthesis, degradation and elimination, or which are associated with hypercholesterolemia, is well summarized in the review article by Kajinami et al. (2004b). According to their review, a statistically significant

Table 1
Mechanisms for direct vascular actions and side effects of statins

Lipid effects
Inhibition of cholesterol biosynthesis Increased uptake and degradation of LDL
Inhibition of LDL oxidation
Inhibition of lipoprotein secretion
Inhibition of modified LDL endocytosis
Antiatherosclerotic effects
Inhibition of migration and proliferation of arterial myocytes
Inhibition of macrophage growth
Inhibition of cholesterol accumulation in macrophages
Inhibition of cell adhesion
Inhibition of tissue factor expression and activity
Inhibition of superoxide generation
Inhibition of endothelin-1 synthesis and expression
Increased expression and activity of eNOS
Increased fibrinolytic activity
Induction of myocytes apoptosis in proliferative lesions
Adverse effects on muscle injury
Reduced cholesterol contents in skeletal muscle cell membranes
Reduced levels of isoprenoids, such as ubiquinone, or regulatory proteins by the inhibition of HMG-CoA reductase
Reduced production of farnesyl pyrophosphate that is required for the activation of small GTP-binding regulatory protein

References: Corsini et al. (1999) and Thompson et al. (2003).

Table 2
Genes previously investigated in pharmacogenetic studies to explore the determinants of statin therapy

Category	Locus	Outcome
Pharmacokinetics	*CYP2C8*	AE
	CYP2C9	AE, LR, PK
	CYP2D6	AE, LR, PK
	CYP3A4	LR, PK
	CYP3A5	LR, PK
	ABCB1 (MDR1)	LR, PK
	ABCC2 (MRP2)	PK
	SLCO1B1 (OATP1B1)	PK
Pharmacodynamics	*ABCA1*	CVDER, LR
	ABCG5/G8	LR
	APOA1	LR
	APOA4	LR
	APOB	LR
	APOE	CVDER, LR
	CYP7A1	LR
	HMGCR	LR
	LDLR	LR
	LIPC	CVDER
	MTP	CVDER, LR
	SCAP	CVDER
Hypothesis-oriented (disease-related)	*ACE*	CVDER
	CETP	CVDER, LR
	ESR1	LR
	FDFT1	LR
	FGB	CVDER
	GP3A	CVDER
	IL6	CVDER
	LEPR	CVDER, LR
	MMP3	CVDER
	PON1	CVDER, LR
	PPARs	LR
	SREBPF1	CVDER, LR
	TLR4	CVDER, LR
	TNFα	CVDER, LR

AE: adverse events; CVDER: cardiovascular event response; LR: lipid response; PK: pharmacokinetics.
Reference: Kajinami et al. (2005).

difference in lipid response was observed associated with the genetic polymorphism in ABCA1, ABCG5/G8, apolipoprotein A1 (APOA1), APOB, APOE, CYP7A1, HMG-CoA reductase and LDL receptor although they sometimes failed to find a statistically significant difference in other studies. Thus, the genetic variation in these factors may influence the pharmacological effect of statins, leading to an interindividual difference in the pharmacological and/or toxic side effects.

3. The mechanism governing the pharmacokinetics of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

3.1. The characteristics of statins

Statins have different pharmacokinetic profiles that are associated with their physicochemical properties. Table 3 shows the log*D* values reflecting the lipophilicity of statins. Simvastatin and lovastatin, which are administered as prodrugs with a lactone ring, have high log*D* values while other statins with open acid structures are less lipophilic. Among them, the log*D* of pravastatin is the lowest. Generally, compounds with high log*D* values can easily cross lipid bilayer membranes by passive diffusion and, thus, distribute to tissues nonspecifically (via passive diffusion). Table 4 shows the inhibitor concentration to produce a 50% inhibition (IC_{50}) of different statins on HMG-CoA reductase. Using purified catalytic fragment of human HMG-CoA reductase and cell-free enzyme system from rat liver, statins directly inhibit this enzyme and, thus, the IC_{50} values obtained in these experimental systems reflect the absolute potency as statins. However, using cell systems to inhibit this enzyme, statins are required to pass through the cell membrane, enter the cells and reach the HMG-CoA reductase in the cells. Thus, the IC_{50} values obtained in these systems reflect the hybrid parameter including membrane permeability of statins and their potency as statins (Table 4). Lipophilic statins such as simvastatin and lovastatin have low IC_{50} values even in the cell systems because they can easily cross the cell membrane via passive diffusion. However, hydrophilic statins (i.e. pravastatin and rosuvastatin) have much higher IC_{50} values than simvastatin and lovastatin in the cell systems except for rat and human hepatocytes although all of these statins have relatively close IC_{50} values in the cell-free systems. This observation supports that hydrophilic statins cannot easily cross the cell membrane. However, they inhibit HMG-CoA reductase potently in rat and human hepatocytes, since these statins are taken up by hepatocytes via active transport systems. The hepatic uptake of statins is described in the following section in detail.

3.2. The mechanism governing the hepatic uptake and biliary excretion of statins

Table 5 shows the pharmacokinetic properties of statins. As all statins available at present are cleared mainly by the liver as shown in Table 5, the processes of the hepatic uptake and biliary excretion as well as the metabolism play important roles in the mechanism governing their total body clearances (CL_{tot}). According to the clearance concept (Rowland et al., 1973; Winkler et al., 1973; Wilkinson & Shand, 1975; Pang & Rowland, 1977; Roberts & Rowland, 1986), hepatic clearance can be described by the following equations in terms of hepatic

Table 3
The log*D* values of statins

	log*D* (pH 7.0)[a]	log*D* (pH 7.4)[b]
Simvastatin (simvastatin acid)	4.4 (1.88)	
Lovastatin (lovastatin acid)	3.91 (1.51)	
Pravastatin	−0.47	−0.75–−1.00
Fluvastatin	1.75	1.00–1.25
Atorvastatin	1.53	1.00–1.25
Cerivastatin	2.32	1.50–1.75
Pitavastatin	1.5	
Rosuvastatin		0.25–−0.50

[a] Ishigami et al. (2001) and Hirano et al. (2005b).
[b] Holdgate et al. (2003).

Table 4
Comparison of IC_{50} values of statins for HMG-CoA reductase activity measured in different experimental systems

Experimental system	IC_{50} values [nM]							Reference
	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Cerivastatin	Atorvastatin	Rosuvastatin	
Cell free systems								
HMG-CoA reductase activity in purified human catalytic fragment of the enzyme (peptide 419–888)	11		44	28	10	8.2	3.5–5.4	1, 2
Cell-free enzyme system from rat liver	1.2	1.2	1.9					3
	2.7		6.9	3.8	3.5	1.2	0.16	1
Hepatocytes								
Primary cultured rat hepatocytes	5.2		5.0	4.8	2.5	0.82	0.30	4
Rat hepatocytes	3.3	4.7	5.2					3
Primary cultured human hepatocytes	8.0	4.1	2.0					5
Non-hepatic cells								
HUVEC (human umblical vein endothelial)	1.0		1900	0.56	3.1	5.5	41	4
	5.5	2.4	1200					5
HCF (human cornea fibroblast)	4.6	15	1300					5
Human skin fibroblasts	2.9	4.0	470					3
NRK-49F (rat fibroblast)	7.9		14000	3.4	1.2	340	310	4
HRPEC (human retinal pigment epithelial cells)	8.0	18	4100					5
HGC (human granulosa cells)	16	27	1500					5
Rat spleen cells	5.3	3.5	170					3
Mouse L-cells	3.8	2.0	1400					3
Rat lenses	23	40	450					3

References: (1) McTaggart et al. (2001), (2) Holdgate et al. (2003), (3) Koga et al. (1990), (4) Buckett et al. (2000), (5) van Vliet et al. (1995).

blood flow (Q_H), blood unbound fraction (f_b) and overall intrinsic clearance ($CL_{int,all}$) of drugs.

(1) Well-stirred model

$$CL_H = \frac{Q_H \cdot f_b \cdot CL_{int,all}}{Q_H + f_b \cdot CL_{int,all}} \quad (1)$$

(2) Parallel-tube model

$$CL_H = Q_H \cdot \left(1 - e^{-\frac{f_b \cdot CL_{int,all}}{Q_H}}\right) \quad (2)$$

(3) Dispersion model

$$CL_H = Q_H \cdot \left\{1 - \frac{4a}{(1+a)^2 \cdot e^{\frac{a-1}{2D_N}} - (1-a)^2 \cdot e^{\frac{a+1}{2D_N}}}\right\} \quad (3)$$

where,

$$a = \sqrt{1 + 4R_N \cdot D_N} \quad (4)$$

$$R_N = \frac{f_b \cdot CL_{int,all}}{Q_H} \quad (5)$$

D_N is a dispersion number and this is taken as 0.17 (Iwatsubo et al., 1996, 1997). $CL_{int,all}$ includes not only metabolism and/or biliary excretion but also the membrane permeability as described by the following equation:

$$CL_{int,all} = PS_{u,influx} \cdot \frac{CL_{int}}{PS_{u,efflux} + CL_{int}} \quad (6)$$

where $PS_{u,influx}$ and $PS_{u,efflux}$ represent the membrane permeability clearance of unbound drugs for the influx and efflux processes, respectively, and CL_{int} represents the 'exact' intrinsic clearance for metabolism and/or biliary excretion of the unbound drugs (Pang & Gillette, 1978; Miyauchi et al., 1993; Yamazaki et al., 1996a; Mizuno et al., 2003). As shown in Eq. (6), the rate-limiting step in $CL_{int,all}$ depends on the relative values of $PS_{u,efflux}$ and CL_{int}. If $PS_{u,efflux}$ is much smaller than CL_{int} ($PS_{u,efflux} \ll CL_{int}$), Eq. (6) gives

$$CL_{int,all} = PS_{u,influx} \quad (7)$$

This equation shows that only the influx process influences $CL_{int,all}$. If $PS_{u,efflux}$ is much larger than CL_{int}, Eq. (6) gives

$$CL_{int,all} = CL_{int} \times \frac{PS_{u,influx}}{PS_{u,efflux}} \quad (8)$$

This equation indicates $CL_{int,all}$ reflects the asymmetry of the membrane permeability (influx/efflux) and the intrinsic metabolic and/or biliary excretion ability. If there is no asymmetry associated with the membrane transport process ($PS_{u,influx} = PS_{u,efflux}$), $CL_{int,all}$ becomes

$$CL_{int,all} = CL_{int} \quad (9)$$

If drugs can rapidly penetrate the cell membrane by passive diffusion, there is no asymmetry associated with the membrane transport and Eq. (9) can be applied. Except for this case, hepatic uptake can be one of the determinants of hepatic clearance.

The specific transporting systems for the hepatic uptake of many drugs including statins have been characterized. These drug transporters can also be caused of drug–drug interactions except for the case where drugs mainly undergo rapid penetration across the cell membrane via passive diffusion (see Eq. (9)). Especially in the case of statins, a transporter-mediated drug–drug interaction in the process of hepatic uptake

Table 5
Pharmacokinetic properties of statins

		Simvastatin		Lovastatin	Pravastatin	Fluvastatin		Atorvastatin	Cerivastatin	Pitavastatin	Rosuvastatin		
	Dose (mg)	40	60	40	40	20	40	40	0.3	2	20	40	80
	Dose form	Lactone	Lactone	Lactone	Open acid	Open acid	Open acid	Open acid	Open acid	Open acid	Open acid	Open acid	Open acid
Acid:	t_{max} (h)	1	4	3	1	0.43–2.1	0.5–1.5	1–2.5	3	1.2	5	5	4–5
	C_{max} (ng/mL)	6.9	3.1	2.7	45–66	53–370	200–440	13–67	3.2	41	6.1	19	39–50
	$t_{1/2}$ (h)	3.5	2.8		1.8–2.0		0.8–2.4	7.8–21	3.2	13		20	17
	AUC (ng h/mL)	25	22	34	110–140	110–440	320–570	58–620	21	120	63	180	310–410
Lactone	t_{max} (h)	4	1	4	2			3	3	1.6	–	5.1	4.5
	C_{max} (ng/mL)	3.2	16	2.8	1.6			4.2	0.30	22			7.1
	$t_{1/2}$ (h)		3.4					8.3	4.8	12			21
	AUC (ng h/mL)	20	47	28	3.3			47	1.9	170			110
	Absorption (%)	60–80		30	34	98		30					
	Bioavailability (%)	<5		5	18	19–29		12	60	80	20		
	Fraction excreted in urine as unchanged form (% of dose)	Negligible		10	47	Negligible		<2	Negligible		<10		

References: Tse et al. (1992), Smith et al. (1993), Kivisto et al. (1998), Muck et al. (1999), Backman et al. (2000), Kyrklund et al. (2001), Backman et al. (2002), Cooper et al. (2003a, 2003b), Klotz (2003), Martin et al. (2003), Schneck et al. (2004), Schachter (2005).

may affect their pharmacological effects because the target organ of statins is the liver, as shown in Section 2.1.

Our research group has studied the mechanism governing the hepatic uptake of statins, especially pravastatin (Yamazaki et al., 1993, 1996b, 1996c; Ishigami et al., 1995). Yamazaki et al. analyzed the mechanism of hepatic uptake and biliary excretion of pravastatin as well as the mechanism of its overall elimination in vivo (Yamazaki et al., 1993, 1996b, 1996c). They clarified that the K_m value for the overall elimination was similar with that for its uptake in isolated hepatocytes but quite different from that for the biliary excretion, estimated from the study using isolated bile canalicular membrane vesilces, suggesting the rate-limiting step for the overall elimination is the hepatic uptake process (Yamazaki et al., 1993, 1996b, 1997). This phenomenon can be explained by the Eq. (7). Yamazaki et al. have shown that pravastatin is selectively distributed to the liver and kidney, with most of it being distributed to the liver (Yamazaki et al., 1996c). Interestingly, liver selective uptake is inhibited by dibromosulphophthaleine but not by *p*-aminohippurate while kidney selective uptake is inhibited both of them. It suggests the different mechanism exists for the uptake of pravastatin in the liver and kidney. Later studies demonstrated that pravastatin uptakes by rat liver and kidney are accounted for by organic anion transporting polypeptides (Oatps) and organic anion transporter 3 (Oat3: gene symbol, *Slc22a8*), respectively (Hsiang et al., 1999; Tokui et al., 1999; Hasegawa et al., 2002).

Table 6
Uptake of statins in isolated or cultured hepatocytes

	K_m [μM]	V_{max} [pmol/min/mg protein]	P_{dif} [μL/min/mg protein]	V_{max}/K_m [μL/min/mg protein]	Ref
Pravastatin	11.5	10.2	0.3	0.887	(1)
Cerivastatin	180	5200*	280*	70*	(2)
	2.6	550*	210*	65*	
	3.7	360*	97*	42*	
Pitavastatin	2.99	79.7	7.73	26.7	(3)
Pravastatin	29.1	546	1.6	18.8	(4)
	36.5	816	1.6	21.5	(5)
Cerivastatin	5.9	260	24	44.4	(6)
Pitavastatin	26.0	3124	1.2	120	(7)

References: (1) Nakai et al. (2001), (2) Shitara et al. (2003), (3) Fujino et al. (2004a), (4) Ishigami et al. (1995), (5) Yamazaki et al. (1993), (6) Hirayama et al. (2000), (7) Shimada et al. (2003).
* per 10 cells.

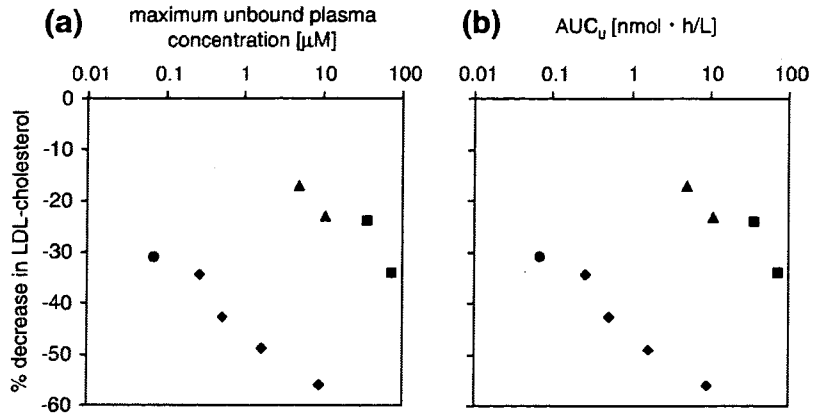

Fig. 3. Relationship between cholesterol-lowering effects of statins and the maximum plasma unbound concentration (**a**) or the area under the plasma unbound concentration–time curve (AUC_u, **b**). Cholesterol lowering effects are expressed as a % reduction in serum LDL-cholesterol. All data are modified from the reported values and the references are shown in Table 7. ◆, ■, ▲ and ● represent plots for atorvastatin, pravastatin, fluvastatin and cerivastatin, respectively.

Table 6 summarizes the reports of the uptake of statins into human or rat hepatocytes. Among the statins shown in Table 6, cerivastatin is taken up avidly by human hepatocytes. Nonspecific uptake, mainly by passive diffusion, is also high for cerivastatin as well as transporter-mediated uptake, possibly due to its lipophilicity. The specific carrier mediated hepatic uptake also contributes to the liver selective distribution (Sirtori, 1993). Table 4 shows that the IC_{50} value of pravastatin for the HMG-CoA reductase inhibition in extrahepatic cells is much higher than that of simvastatin while the values measured in hepatic cells are comparable. It is attributed to the specific uptake of pravastatin into hepatocytes as described above. Atorvastatin and rosuvastatin behave similar to pravastatin, suggesting that they are also taken up into the liver via specific transporters (Table 6). Although cerivastatin is taken up into hepatocytes via transporter-mediated mechanism, it has a marked inhibitory effect on HMG-CoA reductase even in extrahepatic cells. This is attributed to uptake by passive diffusion as cerivastatin is taken up into hepatocytes via passive diffusion as well as a specific transporter-mediated system because it is relatively lipophilic (Table 6). The high uptake of statins specifically by the liver, a target organ, should correlates

Table 7
Comparison of the pharmacological activities of statins in relation to their pharmacokinetics

	f_u	Dose (mg/day)	ΔLDL cholesterol (%)	C_{max} (ng/mL)	$C_{max,u}$ (ng/mL)	AUC (ng h/mL)	AUC_u (ng h/mL)
Atorvastatin	<0.02	10	−38, −30.5	7.41	0.741–1.48	77.6	15.5
		20	−46, −39.2	14.9	1.49–2.98	164	32.8
		40	51, 46.7	27–66.8	2.7–13.2	618	124
		80	54, 57.8	252	25.2–50.4	1293	259
Pravastatin	0.45–0.57	10	19				
		20	24	27	12–16	66	30–38
		40	34	45–66	20–38	140	63–80
Simvastatin	0.02–0.06	10	28				
		20	−35				
		40	−41	10–34			
				6.9 (as a lactone form)		25 (as a lactone form)	
				3.2 (as an open acid form)		20 (as an open acid form)	
		80	−46				
Fluvastatin	<0.01	20	−17	53–370	<3.7	110–440	<4.4
		40	−23	440–450	<4.5	570	<5.7
		80	−36				
Lovastatin	<0.05	20	−29				
		40	−32	10–20			
				2.7 (as a lactone form)		34 (as a lactone form)	
				2.8 (as an open acid form)		28 (as an open acid form)	
		80	−48				
Cerivastatin	<0.01	0.2		1.6–2.0	<0.020	9.5	<0.095
		0.3	31	3.2	0.032	21	<0.21
		0.4	36				
		0.8	45				

Reference: Chong et al. (2001). Data in Table 5 were also referred.

with their pharmacological effects in vivo. Fig. 3 shows the correlation between the unbound plasma concentrations and serum LDL-cholesterol reduction produced by statins (also refer to Table 7). This shows that atorvastatin and cerivastatin exert a higher pharmacological effect at a lower plasma unbound concentration than pravastatin and fluvastatin. It cannot be quantitatively explained by the difference in their affinities for HMG-CoA reductase, which ranges within 6-fold (Table 4) and is, partly, due to their higher hepatic uptake.

Currently, the human transporters involved in the hepatic uptake of statins have been characterized and it has shown that many statins are specifically distributed to the liver via a transporter-mediated system. To date, it has been reported that pravastatin, cerivastatin, pitavastatin, rosuvastatin and atorvastatin are substrates of human OATP1B1 (also refered to as OATP-C/OATP2/LST-1, *SLCO1B1/SLC21A6*) (Hsiang et al., 1999; Nakai et al., 2001; Shitara et al., 2003; Fujino et al., 2004a; Schneck et al., 2004; Kameyama et al., 2005; Lau et al., 2006). Pitavastatin is reported to be also a substrate of OATP1B3 (OATP8/LST-2, *SLCO1B3*, *SLC21A8*) (Hirano et al., 2004). Hirano et al. estimated the contributions of OATP1B1 and 1B3 to the hepatic uptake of pitavastatin by so-called RAF (relative activity factor) method applied to drug metabolism as shown in Fig. 4 (Crespi & Penman, 1997; Hirano et al., 2004). This result suggests that pitavastatin is predominantly taken up into human hepatocytes via OATP1B1 with a minor contribution of OATP1B3. Simvastatin and lovastatin inhibit OATP1B1-mediated transport, suggesting that they may also be substrates of OATP1B1 (Hsiang et al., 1999). However, the contribution of this transporter to the hepatic uptake of simvastatin and lovastatin seems to be low because these lactone statins are lipophilic and are taken up by hepatocytes, and even by other tissues, by passive diffusion (Sirtori, 1993).

Our research group also examined the biliary excretion mechanism of statins, especially for pravastatin (Yamazaki et al., 1996d, 1997; Niinuma et al., 1999). Our investigations suggest that pravastatin is efficiently excreted into the bile via transporters, and then subsequently eliminated. Comparative studies involving normal rats and Eisai hyperbilirubinemic rats (EHBR), whose multidrug resistance associated protein 2 (Mrp2, *Abcc2*) is hereditarily deficient, showed that pravastatin is a substrate of Mrp2 (Yamazaki et al., 1996d, 1997). Thus, pravastatin is efficiently transported via transporters associated with hepatic uptake and biliary excretion and, both transporters for uptake and excretion help its specific distribution to the liver (Fig. 5). In humans, Sasaki et al. showed that pravastatin is a substrate of MRP2 (*ABCC2*), a counterpart of rat Mrp2, using a double transporter (OATP1B1 and MRP2) expressing system

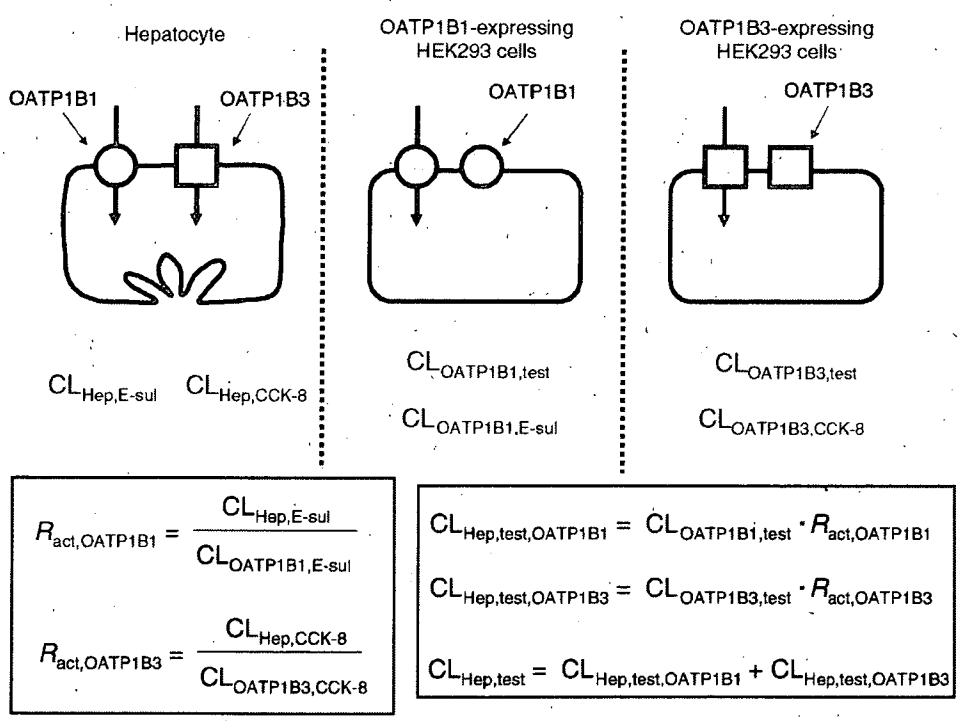

Fig. 4. Estimation of the contributions of OATP1B1 and OATP1B3 to the hepatic uptake of test compounds using selective substrate for each of transporters. The method for estimating the contribution of each transporter (OATP1B1 and 1B3) to the total hepatic uptake using reference compounds which are selectively taken up by a single transporter, OATP1B1 or 1B3, is shown. The uptake clearances of test compounds by OATP1B1 and 1B3 in human hepatocytes ($CL_{Hep,test,OATP1B1}$ and $CL_{Hep,test,OATP1B3}$) can be estimated by comparison with the uptake of reference compounds. Estrone 3-sulfate (E-sul) and cholecystokinine octapeptide (CCK-8) are used as selective substrates for OATP1B1 and 1B3, respectively. $CL_{Hep,E\text{-}sul}$ and $CL_{Hep,CCK\text{-}8}$ represent the uptake clearances of E-sul and CCK-8 in human hepatocytes, respectively, and $CL_{OATP1B1,E\text{-}sul}$ and $CL_{OATP1B3,CCK\text{-}8}$ represent the uptake clearances of E-sul and CCK-8 in OATP1B1- and 1B3-expressing HEK293 cells, respectively. $R_{act,OATP1B1}$ and $R_{act,OATP1B3}$ are ratio of the uptake clearances of reference compounds in human hepatocytes to those in transporter-expressing cells. The uptake clearance of test compounds mediated by OATP1B1 or 1B3 can be estimated by multiplying the uptake clearance of test compounds in transporter expressing cells by the R_{act} value for OATP1B1 or 1B3, respectively, as shown in the figure.

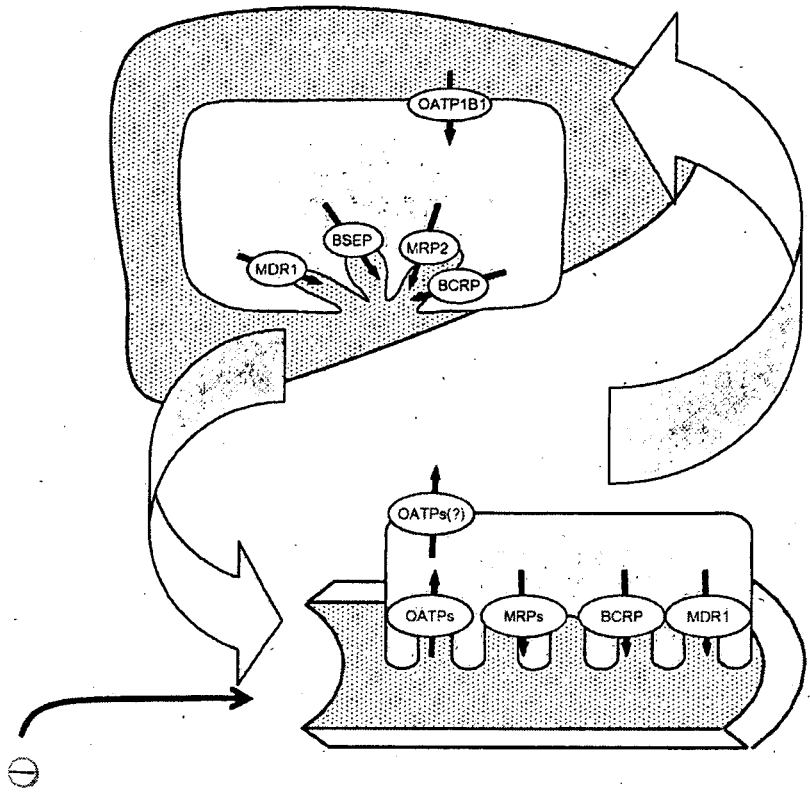

Fig. 5. Liver-selective distribution of pravastatin by transporters in the liver and intestine. Pravastatin is taken up into the liver via transporters including OATP1B1 and excreted into the bile via multiple transporters including MRP2, BCRP, MDR1 and BSEP in the unchanged form although the contribution of MRP2 seems to be the highest among the transporters on the bile canalicular membrane. The excreted pravastatin passes into the intestine and its absorption into the blood is mediated by transporters. OATP2B1 has recently been reported to be one of the transporters responsible for the intestinal absorption although its contribution to the intestinal absorption is unknown. Other members of the OATP family may also be involved in its absorption. Most of the other open-acid statins are also substrates of these transporters. These transporters may also be involved in the selective disposition of other statins to the liver.

(Sasaki et al., 2002). More recently, Matsushima et al. clarified multidrug resistance 1 (MDR1, *ABCB1*) and breast cancer resistance protein (BCRP, *ABCG2*) as well as MRP2 are involved in the biliary excretion of pravastatin and cerivastatin although their contributions are not estimated (Matsushima et al., 2005; Fig. 6). For pravastatin, MRP2 has the most potent transport activity among these efflux transporters while, for cerivastatin, MDR1 and MRP2 have relatively higher transport activity in their experimental systems (Matsushima et al., 2005). Hirano et al. reported that pitavastatin is also a substrate of human BCRP, MDR1 and MRP2 (Hirano et al., 2005a). On the other hand, in the case of experimental animals, its biliary excretion was not changed either in EHBR or Mdr1a/1b (*Abcb1a/1b*) knock-out mice compared with the corresponding wild type animals (Fujino et al., 2002). On the other hand, the biliary excretion of pitavastatin was extensively decreased in Bcrp (*Abcg2*) knock-out mice (Hirano et al., 2005a). In addition, Hirano et al. showed that human and rat bile salt exporting pump (BSEP/Bsep, *ABCB11/Abcb11*) also accept pravastatin as their substrates while they do not accept cerivastatin, fluvastatin and pitavastatin (Hirano et al., 2005b). These reports suggest that biliary excretion of statins is mediated by multiple transporters. Table 8 summarizes the human and rat transporters involved in the transport of statins.

3.3. Cytochrome P450-mediated metabolism

Statins, which are metabolized by members of the cytochrome P450 (P450), are susceptible to metabolism-mediated drug–drug interactions. Different drugs affect the pharmacokinetics of statins, depending on the isoforms of P450 that are involved in their metabolism. Simvastatin, lovastatin and atorvastatin are predominantly metabolized by cytochrome P450 3A4 (CYP3A4) (Wang et al., 1991; Prueksaritanont et al., 1997; Lennernas, 2003). On the other hand, fluvastatin is metabolized by CYP2C9, which is unique among statins (Transon et al., 1995, 1996). Pravastatin and rosuvastatin undergo very little metabolism by P450 and, therefore, they are not susceptible to the drug–drug interactions involving metabolism (Hatanaka, 2000; McCormick et al., 2000; White, 2002). Pitavastatin undergoes a minor degree of metabolism by CYP2C9, but the rate of metabolism is very slow and P450-mediated metabolism does not play an important role in its elimination (Fujino et al., 2004b). Thus, also for pitavastatin, P450-mediated metabolism is not susceptible to the mechanism governing drug–drug interactions. Cerivastatin is metabolized by 2 different P450 isoforms: CYP2C8 and 3A4 (Muck, 2000). Because of this dual metabolic pathway, it was believed to be less likely to be affected by a drug–drug interaction. In fact, its

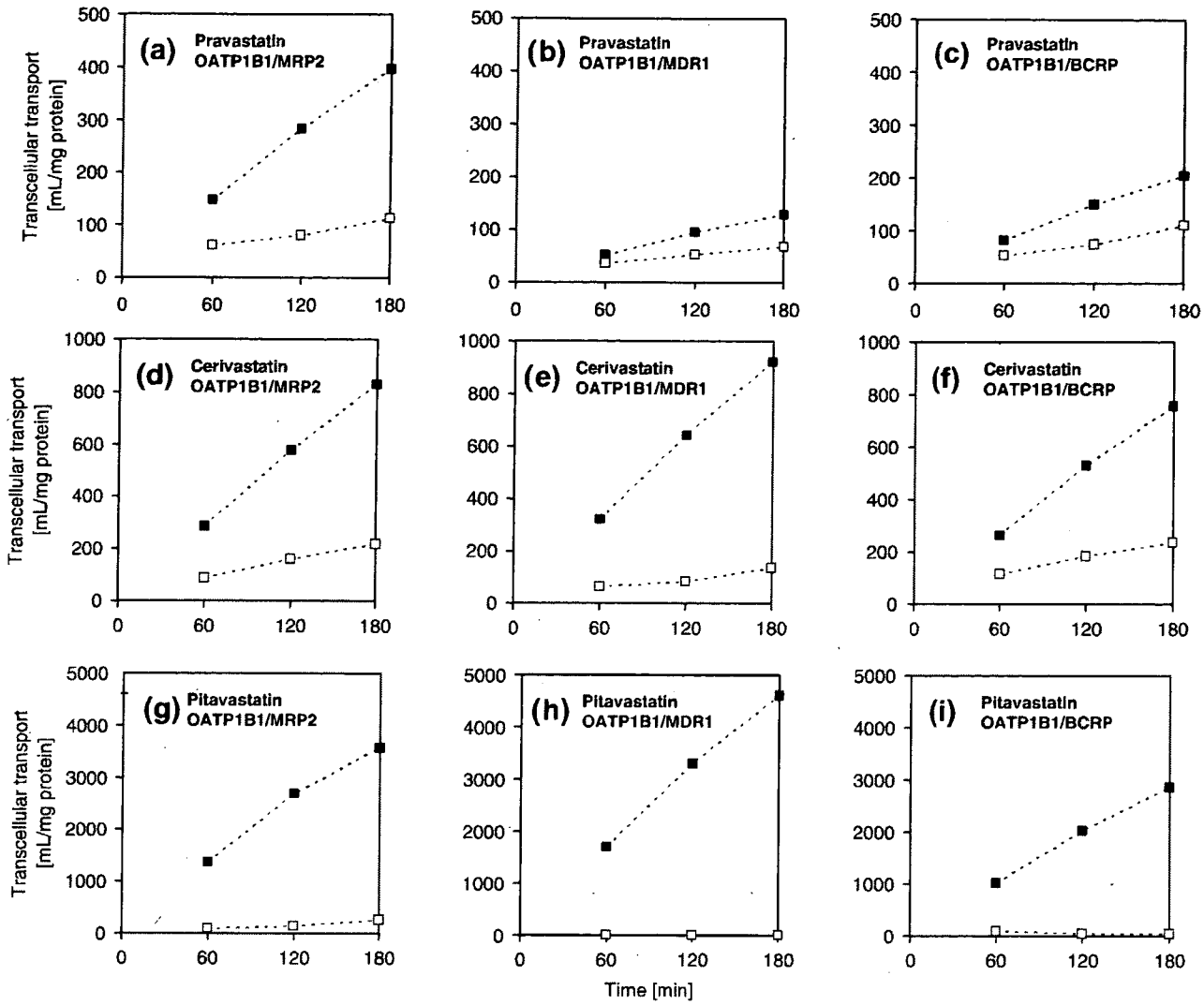

Fig. 6. Transcellular transport of pravastatin, cerivastatin and pitavastatin in OATP1B1/BCRP, OATP1B1/MDR1 and OATP1B1/MRP2 double expressing MDCK II cells. Transcellular transport of pravastatin (**a**, **b**, **c**), cerivastatin (**d**, **e**, **f**) and pitavastatin (**g**, **h**, **i**) in OATP1B1/BCRP (**a**, **d**, **g**), OATP1B1/MDR1 (**b**, **e**, **h**) and OATP1B1/MRP2 (**c**, **f**, **i**) is shown. All transport was measured bidirectionally and □ and ■ represent the apical-to-basal and basal-to-apical transports, respectively. Basal-to-apical transport of statins was enhanced by the expression of BCRP, MDR1 and MRP2 compared with the transport in OATP1B1 single expressing cells, suggesting they are substrates of these hepatic efflux transporters. Reprint from "Identification of the hepatic efflux transporters of organic anions using double-transfected Madin-Darby canine kidney II cells expressing human organic anion-transporting polypeptide 1B1 (OATP1B1)/multidrug resistance-associated protein 2, OATP1B1/multidrug resistance 1, and OATP1B1/breast cancer resistance protein" by Matsushima et al., 2005, and "Involvement of BCRP (ABCG2) in the biliary excretion of pitavastatin" by Hirano et al., 2005, with the permissions from the American Society for Pharmacology and Experimental Therapeutics.

plasma concentration is not affected by coadministration of itraconazole and erythromycin, potent inhibitors for CYP3A4 (Muck et al., 1998; Kantola et al., 1999; Mazzu et al., 2000). However, this phenomenon appears to be only due to the smaller contribution of CYP3A4 compared with that of CYP2C8 and, thus, this statin is also susceptible to the drug–drug interactions during the process of CYP2C8-mediated metabolism (Shitara et al., 2004). Table 9 shows the metabolic rates of statins (open acid and lactone forms) in human liver microsomes reported by Fujino et al. (2004c). It also shows P450 isoforms involved in their metabolism (Fujino et al., 2004c).

3.4. UDP glucuronosyl transferase-mediated lactonization of statins

Recently, a possible metabolic pathway leading to the lactone form of statins via UDP glucuronosyl transferase (UGT)-mediated glucuronidation was reported (Prueksaritanont et al., 2002a; Fujino et al., 2003). HMG-like moieties of open acid statins are glucuronosylated by UGT (UGT1A1 and 1A3), subsequently followed by lactonization of the acyl glucuronide HMG-like moieties (Fig. 7). This mechanism of lactonization, via acyl glucuronide, is common metabolic pathway for all statins with the open acid form. Due to this metabolic pathway, statins

Table 8
Transport profile of statins in transporter expression systems

	Transporter name	K_m[a] [μM]	Expression systems
(a) Human transporters			
Atorvastatin	OATP1B1	12.4	HEK293 cells
Pravastatin	OATP1B1	33.7	293c18 cells
Pravastatin	OATP1B1	11.5	*Xenopus laevis* oocytes
Pravastatin	OATP1B1	85.7	HEK293 cells
Cerivastatin	OATP1B1	+	MDCK II cells
Pitavastatin	OATP1B1	3.0	HEK293 cells
Rosuvastatin	OATP1B1	8.5	*Xenopus laevis* oocytes
Pitavastatin	OATP1B3	3.25	HEK293 cells
Pravastatin	OATP2B1	2250	HEK293 cells
Pravastatin	OAT3	+	S_2 cells
Pravastatin	MDR1 (ABCB1)	+	MDCK II cells (Double transfected cells)
Cerivastatin	MDR1 (ABCB1)	+	MDCK II cells (Double transfected cells)
Cerivastatin	MDR1 (ABCB1)	+	LLC-PK1 cells
Pravastatin	MRP2 (ABCC2)	+	MDCK II cells (Double transfected cells)
Cerivastatin	MRP2 (ABCC2)	+	MDCK II cells (Double transfected cells)
Pravastatin	BCRP (ABCG2)	+	MDCK II cells (Double transfected cells)
Cerivastatin	BCRP (ABCG2)	+	MDCK II cells (Double transfected cells)
Pravastatin	BSEP	124	membrane vesicles from HEK293 cells
Cerivastatin	BSEP	–	membrane vesicles from HEK293 cells
Fluvastatin	BSEP	–	membrane vesicles from HEK293 cells
Pitavastatin	BSEP	–	membrane vesicles from HEK293 cells
(b) Rat transporters			
Pravastatin	Oatp1a1	30	293c18 cells
Pravastatin	Oatp1a4		293c18 cells
Pravastatin	Oatp1a4	37.5	*Xenopus laevis* oocytes
Pravastatin	Oatp4	+	MDCK II cells (Double transfected cells)
Cerivastatin	Oatp14	1.34	HEK293 cells
Pravastatin	Oatp14	+	HEK293 cells
Pravastatin	Oat3	13.4	LLC-PK1 cells
Pravastatin	Bsep	+	membrane vesicles from HEK293 cells
Cerivastatin	Bsep	–	membrane vesicles from HEK293 cells
Fluvastatin	Bsep	–	membrane vesicles from HEK293 cells
Pitavastatin	Bsep		membrane vesicles from HEK293 cells

Reference: TP-search (http://www.TP-search.jp/).
[a] +, transported but no report of K_m value; –, not transported.

can be metabolized by the multiple pathways shown in Fig. 7: lactonized statins may be converted to the open acid form again by carboxy esterase and, subsequently, metabolized or excreted into the bile or urine, or directly metabolized by P450 as the lactone forms. Table 9 shows the rate of UGT-mediated glucuronidation of different statins. The lactone forms of statins are more rapidly metabolized by P450 than the open acid forms (Table 9). It may suggest that there is a metabolic pathway of lactonized statins mediated by P450 after the UGT-mediated lactonization. Prueksarinont et al. have shown that gemfibrozil, a fibrate, inhibited the P450- and UGT-mediated metabolism of simvastatin, atorvastatin and cerivastatin (Prueksaritanont et al., 2002b). In addition, when coadministered with gemfibrozil, the plasma concentration of simvastatin acid increased while the area under the plasma concentration–time curve (AUC) of the lactone form of simvastatin was reduced in dogs, suggesting that gemfibrozil inhibits the lactonization of simvastatin in vivo (Prueksaritanont et al., 2002b). But the metabolic rates by UGT are 7.2- to 71-fold lower than those mediated by P450 except for pitavastatin (Table 9) and, thus, this metabolic pathway is not likely to cause a serious interaction. For pitavastatin, biliary excretion of the intact form is the main elimination pathway in some experimental animals including rats, rabbits and dogs (Kojima et al., 1999), suggesting that the UGT-mediated lactonization makes only a minor contribution to the total body clearance.

3.5. Urinary excretion

Generally, urinary excretion of statins is low (Table 5). However, it is not negligible for pravastatin, since 40–47% of intravenously administered drug is excreted in the urine in humans (Hatanaka, 2000). Yamazaki et al. have shown that pravastatin undergoes renal uptake in rats although urinary excretion is low (Yamazaki et al., 1996c). In addition, more recent studies have shown that pravastatin is a substrate of rat Oat3 and human OAT3 (*SLC22A8*), which are involved in the renal uptake of drugs (Hasegawa et al., 2002; Takeda et al., 2004). In rats, the K_m value for the uptake of pravastatin in rat kidney slices was similar with that in rat Oat3-expressing LLC-PK_1 cells (Hasegawa et al., 2002). In addition, the inhibition studies of the uptake of pravastatin by *p*-aminohippurate (a relatively selective inhibitor of rat Oat1), benzylpenicillin (a relatively selective inhibitor of rat Oat3) and dibromosulfophthalein (a nonspecific inhibitor of rat Oat1 and Oat3) revealed that their K_i were similar in rat kidney slices and Oat3-expressing cells (Hasegawa et al., 2002). These results strongly support that its renal uptake is mediated by Oat3 (Hasegawa et al., 2002). Also in humans, OAT3 may be involved in the urinary excretion of pravastatin. Although Nishizato et al. failed to find a relationship between SNPs in human OAT3 and the pharmacokinetics of pravastatin, this does not rule out the contribution of human OAT3 to the elimination of this statin (Nishizato et al., 2003). The plasma concentration of pravastatin is affected by coadministration of gemfibrozil (Kyrklund et al., 2003). In this study, gemfibrozil reduced the renal clearance of pravastatin although the contribution of this reduction in urinary excretion to that in the total body clearance is minor and, thus, reduced renal clearance cannot fully explain the total pharmacokinetic alteration (Kyrklund et al., 2003). But, this observation supports the involvement of a transport system in the urinary excretion of pravastatin, which is inhibited by gemfibrozil.

3.6. Intestinal absorption and excretion

All statins currently on the market are well absorbed from the intestine. The mechanism for the intestinal absorption of statins

Table 9
P450- and UGT-mediated metabolism of statins in human liver microsomes

	P450-mediated metabolism for open acid forms		P450-mediated metabolism for lactone forms		UGT-mediated metabolism		
	CL_{int} (μL/min/mg protein)	Isoforms	CL_{int} (μL/min/mg protein)	Isoforms	CL_{int} ($=V_{max}/K_m$) (μL/min/mg protein)	K_m (μM)	V_{max} (pmol/min/mg protein)
Simvastatin	28.4	CYP3A4	1960	CYP3A4	0.4	416	162
Fluvastatin	33.2	CYP2C9 CYP3A4[a]	226	CYP3A4			
Cerivastatin	20.8	CYP2C8 CYP3A4	622	CYP3A4	2.9	8	238
Atorvastatin	26.0	CYP3A4	1890	CYP3A4	3.3	16	52
Pitavastatin	2.50	CYP2C9[a] CYP2C8[a]	5.40	CYP3A4 CYP2D6[a]	3.1	78	237

Reference: Fujino et al. (2004c).
[a] Involved but to a small extent; –, no data.

varies from one drug to another. Simvastatin and lovastatin, which are lipophilic, can easily penetrate the plasma membrane in a nonspecific manner while others may be recognized by specific transport system(s). Tamai et al. reported that pravastatin is taken up into rabbit intestinal brush border membrane vesicles by coupled transport with protons (Tamai et al., 1995). They also reported that it takes place more via specific transport than by passive diffusion (Tamai et al., 1995). It is inhibited by monocarboxylic acids, acetic acid and nicotinic acid, suggesting that this statin is also transported by a transporting system for monocarboxylic acids (i.e. MCT (monocarboxylic acid transporter)). However, to date, there have been no reports that pravastatin is a substrate of MCT. Recently, pravastatin was reported to be a substrate of OATP2B1 (OATP-B, *SLCO2B1/SLC21A9*), which is expressed in the intestine (Kobayashi et al., 2003; Nozawa et al., 2004). OATP2B1-mediated transport is reported to depend on the pH of the incubation buffer, and this agrees with the results of in vivo studies in rats (Tsuji, 1999). Although OATP2B1 is a candidate for one of the transporters involved in the intestinal absorption of pravastatin, its function in vivo has not been determined yet. However, we examined the uptake of pravastatin into rat everted sacs and found that it was comparable with that of polyethylene glycol 4000 (PEG4000), suggesting the minimal contribution of transporter-mediated absorption for pravastatin in rats (unpublished data; Fig. 8). On the other hand, a higher transport of cerivastatin was observed than PEG4000 and it was saturable (Fig. 8). The intestinal absorption of cerivastatin may, thus, be mediated by some transporter(s). If transporter-mediated intestinal transport takes place, intestinal absorption can be affected by coadministered drugs and is also a target for drug–drug interactions. It has been

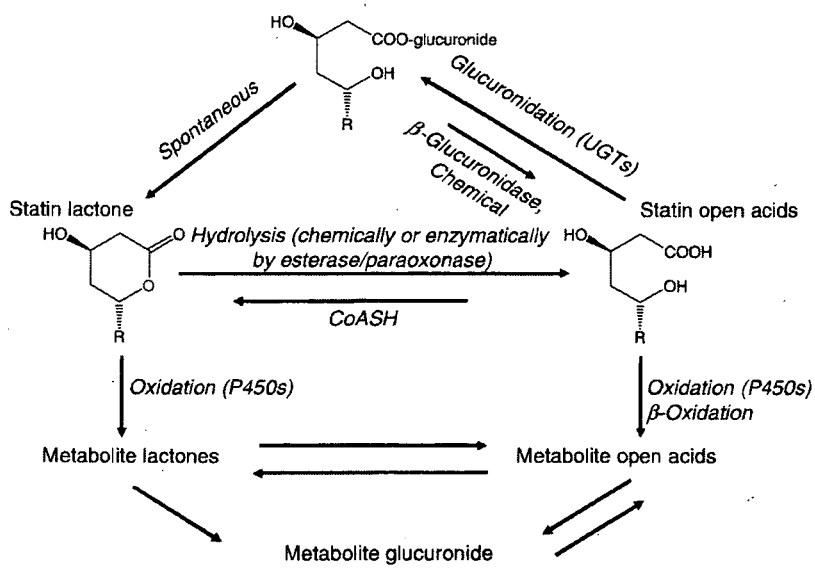

Fig. 7. Lactonization of statins mediated by UDP-glucuronosyl transferase. This scheme was originally proposed by Prueksaritanont et al. (2002a). The statins have an acid/lactone interconversion pathway and are metabolized by a complex mechanism. The statin lactones are hydrolyzed to their open acids chemically or enzymatically by esterases or paraoxonases. The statin acids are converted to the corresponding lactones by the acyl glucuronide intermediate and by the CoASH-dependent pathway. Both acyl glucuronide and acyl CoA derivatives may revert to the statin acids by hydrolysis. Reprint from "Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization" by Prueksaritanont et al., 2002a, with the permission from the American Society for Pharmacology and Experimental Therapeutics.

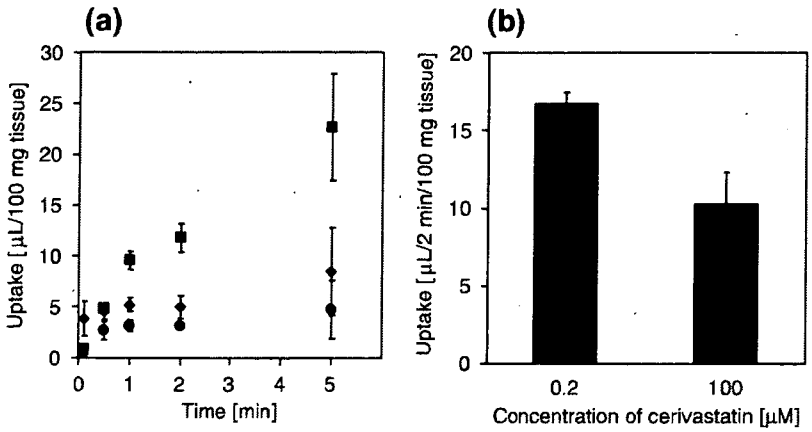

Fig. 8. Uptake of pravastatin and cerivastatin in rat jejunum everted sacs (a) and dose dependence of the cerivastatin uptake (b) (Kawakami-Takada, Hiroyuki Kusuhara & Yuichi Sugiyama, unpublished results). (a) The uptake of [^{14}C]cerivastatin (0.2 μM, ■) [^{3}H]pravastatin (1 μM, ◆) or [^{14}C]PEG4000 (●) in rat jejunum everted sacs is shown. Each point represents the mean±S.E. (n=3) using everted sacs from different rats. Time-dependent uptake of statins was observed but the uptake of pravastatin was not higher than that of PEG4000 while that of cerivastatin was higher. (b) The uptake of [^{14}C]cerivastatin in rat jejunum everted sacs at 2 min at 37 °C was examined at the concentrations of 0.2 and 100 μM. Specific uptake was observed by the subtraction of simultaneously determined [^{3}H]PEG4000 uptake from the total uptake of cerivastatin. Each data point represents the mean±S.E. (n=3).

shown that the intestinal absorption of fexofenadine is reduced by the concomitant intake of orange, grapefruit and apple juices (Dresser et al., 2002; Dresser et al., 2005). In addition, these fruit juices inhibit the OATP1A2 (OATP-A, *SLCO1A2/SLC21A3*) mediated uptake of fexofenadine although the expression and function of OATP1A2 in the intestine is unknown (Dresser et al., 2002, 2005). These observations may suggest a possibility of transporter-mediated drug–drug interactions (Dresser et al., 2002, 2005). More recently, Satoh et al. reported that citrus juice (i.e. grapefruit and orange juice) but not apple juice inhibited OATP2B1-mediated transport (Satoh et al., 2005). However, grapefruit juice does not affect the pharmacokinetics of pravastatin while it increases the plasma concentration of atorvastatin, which is possibly the result of a CYP3A4-mediated drug–drug interaction (Lilja et al., 1999; Fukazawa et al., 2004). The result obtained with the combination of grapefruit juice and pravastatin suggests that this interaction was not caused by a transporter-mediated process. To clarify the mechanism of drug–drug interactions involved in the intestinal absorption of statins, more details are required about the molecular mechanism of their intestinal absorption including the functions and contributions of transporters to the intestinal absorption of statins. Contributions of each transporter also need to be clarified.

Simvastatin, lovastatin, pravastatin, cerivastatin, atorvastatin and pitavastatin are substrates of P-glycoprotein (P-gp) (Sakaeda et al., 2002; Hochman et al., 2004; Kivisto et al., 2004a; Matsushima et al., 2005). Although pravastatin was reported not to be a substrate of MDR1 by Hirai et al. (2001), Wang et al. (2001) and Sakaeda et al. (2002), it was shown to be a moderate substrate of MDR1 by Matsushima et al. (2005). Although Matsushima et al. observed the MDR1-mediated transport of pravastatin, its transcellular transport mediated by OATP1B1 and MDR1 was lower than those of cerivastatin and pitavastatin (Matsushima et al., 2005). The pharmacokinetics of statins, which are substrates of P-gp, may be affected by P-gp inhibitors and their bioavailability may be increased. However, for statins with relatively high bioavailability, their plasma concentration is not that much affected by P-gp inhibitors. As the bioavailability of cerivastatin is about 60%, the increase in its plasma concentration by inhibition of P-gp-mediated intestinal efflux does not exceed 5/3-folds of that of the controls. Thus, cerivastatin is less likely to exhibit a serious interaction with P-gp inhibitors.

3.7. Distribution to the central nervous system

One of the side effects of statins is sleep disturbance (Schaefer, 1988; Barth et al., 1990). The distribution of statins to the central nervous system (CNS) may cause such a side effect. On the other hand, increasing data suggest that statins have properties that are potentially neuroprotective, that is, endothelial protection via actions on the nitric oxide synthase system, as well as antioxidant, anti-inflammatory and antiplatelet effects (Cucchiara & Kasner, 2001). Thus, statins can be used also for the treatment of CNS diseases. Increasing the access of statins to the brain may improve the therapeutic effects in the CNS although it may also increase their incidence of CNS side effects. Although simvastatin and lovastatin cause a sleep disturbance, pravastatin does not, indicating that simvastatin and lovastatin can easily penetrate the blood–brain barrier while pravastatin does not (Saheki et al., 1994). Comparison of pitavastatin and pravastatin suggests that the brain-to-plasma concentration ratio of pitavastatin is lower than that of pravastatin although pitavastatin is more lipophilic than pravastatin (Kikuchi et al., 2004; Table 3). The lower distribution of pitavastatin to the brain strongly supports the existence of efflux transporter(s). Kikuchi et al. analyzed the mechanism of efflux of statins from the CNS in rats and found a saturable and inhibitable efflux transport system for both of pitavastatin and pravastatin from the CNS, suggesting the existence of efflux transporting system(s) (Kikuchi et al., 2004). Their analyses also suggest that multiple transporters including rat

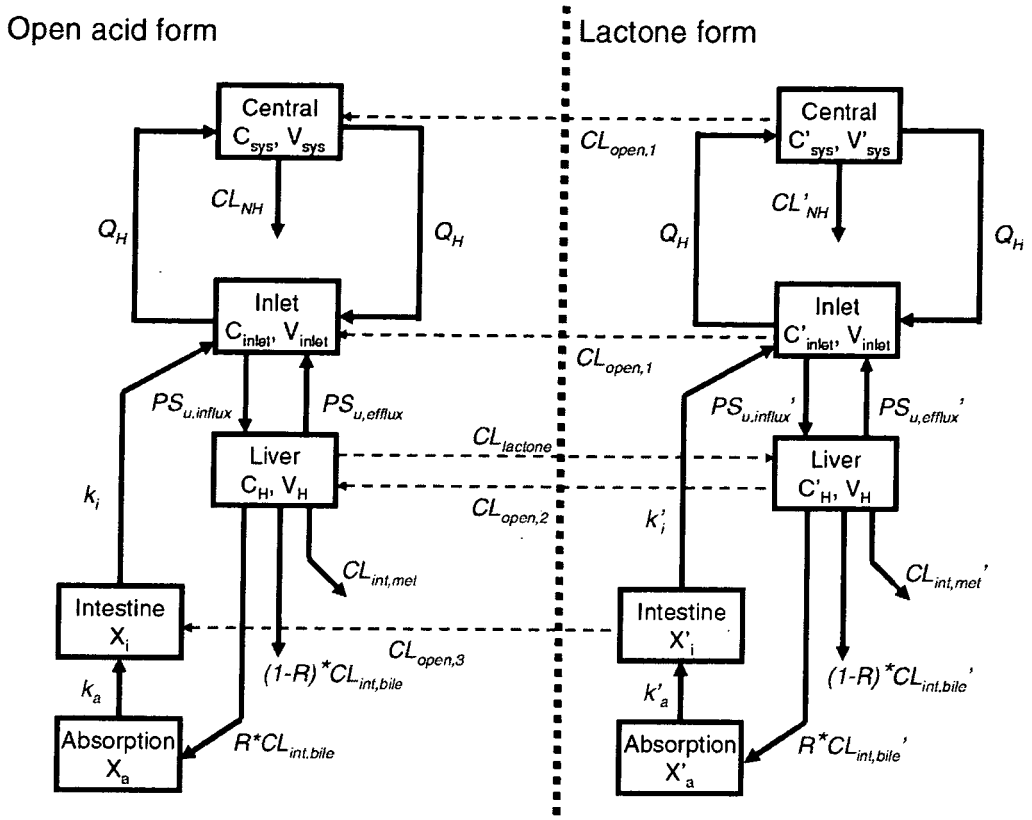

Fig. 9. A physiologically based pharmacokinetic model to describe the disposition of statins. Our analyses of statin disposition were performed using this physiologically based pharmacokinetic model. The meaning of all the parameters is given in Table 10. Because statins have an interconversion pathway between the lactones and open acids, the compartment for statins with open acids and lactones is separately described. In the present analysis, we have assumed that open acid statins are converted to lactones mainly via an acyl glucuronide intermediated pathway, mediated by UGT in the liver.

Oatp1a4 (Oatp2, *Slco1a4/Slc21a5*) and Oat3 are involved in the efflux of these statins from the CNS (Kikuchi et al., 2004). This process may also be inhibited by the coadministered drugs, resulting in the alteration of their therapeutic or side effects in the CNS.

3.8. Distribution to the skeletal muscle

One of the serious adverse effects of statins is myotoxicity including serious myopathy and rhabdomyolysis. Recently, there has been a report regarding the transporter which recognizes statins as its substrate localized in muscle (Takeda et al., 2004). Takeda et al. reported that OAT1 (*SLC22A6*) and OAT3 are expressed in muscle and OAT3 mediates the pravastatin transport (Takeda et al., 2004). They also observed that pravastatin, fluvastatin and simvastatin inhibit OAT1- and 3-mediated transport although the IC_{50} values are higher than their therapeutic concentrations in clinical situations (Takeda et al., 2004). OAT3 may be responsible for the myotoxicity of statins which are its substrates, especially in the case of statins of low lipophilicity. However, to date, there have not been any reports of the transporter-mediated saturable and inhibitable transport of statins to muscle. Thus, we cannot conclude that transporters mediate the uptake of statins by muscle and it is also unclear whether the transport of statins to muscle may be a target for drug–drug interactions or not.

3.9. Elimination mechasnisms

In this section, elimination mechanism for each statin is summarized. The target for drug–drug interactions is also provided here.

3.9.1. Simvastatin and lovastatin

Simvastatin and lovastatin are lipophilic statins with lactone forms, which easily cross the plasma membrane and, thus, they are easily absorbed from the intestine. However, they are substrates of CYP3A4 and P-gp with high affinities. CYP3A4 and P-gp are expressed in the liver and intestine and play an important role in the clearance in these tissues. Especially in intestine, these 2 systems coordinately work in drug detoxification and, thus, most of drugs, which are their bisubstrates, are well metabolized in intestine and their gut extraction is high (Benet et al., 1999). In part due to this mechanism, the bioavailabilities of these statins are low (<5 and 5% for simvastatin and lovastatin, respectively). Inhibition of CYP3A4 and/or P-gp may result in the increased absorption and cause a drug–drug interaction. In addition, mainly they are eliminated from the liver by the CYP3A4-mediated metabolism and, so, they are susceptible to CYP3A4-mediated drug–drug interactions also in the drug elimination process.

3.9.2. Pravastatin, rosuvastatin and pitavastatin

Pravastatin and rosuvastatin are not metabolized by P450. Although pitavastatin is metabolized by CYP2C9 in vitro, its metabolic rate is quite low. These statins are mainly eliminated from the body by a transporter-mediated excretion mechanism in the liver. Because they are substrates of OATP1B1, they are extensively taken up by the liver. In the particular case of pravastatin, a number of studies have investigated its transport mechanism. These suggest that enterohepatic recirculation contributes to its liver-specific distribution as shown in Fig. 5. For these statins, although P450-mediated drug–drug interactions are not possible, they are likely to be affected by transporter-mediated drug–drug interactions.

3.9.3. Fluvastatin

Fluvastatin is metabolized mainly by CYP2C9. It is unique among statins that are eliminated mainly by metabolism. This statin is not affected by CYP3A4 inhibitors although it is susceptible to CYP2C9-mediated drug–drug interactions. As fluvastatin is also a statin with a low lipophilicity, it is possible that some transport systems are involved in its hepatic uptake.

3.9.4. Cerivastatin

As this statin is no longer on the market, this information is of no clinical use. However, as this statin has some special characteristics, we will provide information about this statin. Cerivastatin is metabolized by 2 different enzymes, CYP2C8 and 3A4. This dual metabolic pathway is unique among statins. However, their estimated contributions are 61% and 37%, respectively (Shitara et al., 2004), and, due to the major contribution of CYP2C8, it is susceptible to CYP2C8-mediated drug–drug interactions. Generally, drugs, which have multiple metabolic pathways, are less susceptible to severe drug–drug interactions. However, if a contribution of 1 enzyme or transporter is relatively high, drug–drug interactions involving the process of metabolism or transport should be possible. As cerivastatin is a substrate of OATP1B1, transporter-mediated drug–drug interactions can also occur.

3.9.5. Atorvastatin

This statin also undergoes to CYP3A4-mediated metabolism. However, this hydrophilic statin is a substrate of OATP1B1 and actively taken up into the liver (Kameyama et al., 2005; Lau et al., 2006) prior to the metabolism. Lau et al. showed that saturable transport system involves in the hepatic uptake of atorvastatin in rats in vivo and it is inhibited by probenecid (Lau et al., 2006). As described in the Section 3.2, its clearance is affected not only by the metabolic rate but by the uptake rate (see Eq. (6)). This statin may be susceptible to the CYP3A4- and OATP1B1-mediated drug–drug interaction.

4. Model analysis of pharmacokinetic alterations of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

In Section 3, some factors affecting the pharmacokinetics of statins were reviewed. In this section, we present some quantitative analyses of the effects of these factors (i.e. the increase or decrease in metabolic or transport rates) based on a physiological model. A physiological model based analysis is useful for the quantitative estimation of the impact of these factors on the plasma concentration or AUC. Here, we have carried out an analysis based on a physiological model as shown in Fig. 9 and Table 10. In this model, drug elimination from the liver is described by a hybrid process of uptake ($PS_{u,influx}$) and efflux

Table 10
Parameters used in the physiologically based pharmacokinetic model

Q_H	hepatic blood flow
C_H	concentration of statins in the liver
C_{inlet}	concentration of statins at the inlet to the liver
C_{sys}	concentration of statins in the circulating blood
X_a	total amount of statins pooled for the intestinal absorption
X_i	total amount of statins in the epithelial cells in the intestine
V_H	volume of liver
V_{inlet}	volume of inlet to the liver
V_{sys}	distribution volume of statins in the central compartment
$PS_{u,influx}$	permeability square product for the hepatic uptake of statins
$PS_{u,efflux}$	permeability square product for the efflux of statins across the sinusoidal membrane
CL_{int}	$CL_{int,met}+CL_{int,bile}$
$CL_{int,met}$	intrinsic clearance of statins for the hepatic metabolism
$CL_{int,bile}$	intrinsic clearance of statins for the biliary excretion
R	fraction of statins reabsorbed after biliary excretion
$CL_{open,1}$	clearance for conversation to the open acid form in the blood (including central compartment and inlet to the liver)
$CL_{open,2}$	clearance for conversion to the open acid form in the liver
$CL_{open,3}$	clearance for conversion to the open acid form in the intestine
$CL_{lactone}$	clearance for conversion to the lactone form in the liver
K_i	rate constant for the absorption from the intestinal epithelium to the hepatic portal vein
K_a	rate constant for the absorption from the intestinal lumen into the epithelium
f_u	protein unbound fraction in the circulating blood
f_i	protein unbound fraction in intestine
f_h	protein unbound fraction in liver

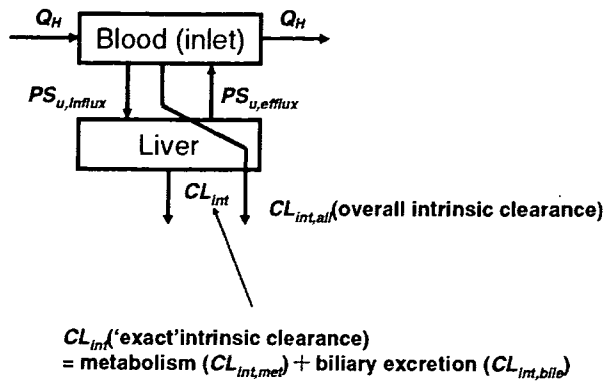

Fig. 10. Compartment model to describe elimination from the liver. The elimination from the liver can be described by the hybrid process of uptake ($PS_{u,influx}$) and efflux ($PS_{u,efflux}$) across the sinusoidal membrane and biliary excretion at the bile canalicular membrane ($CL_{int,bile}$) and/or metabolism ($CL_{int,met}$). CL_{int} represents the summation of $CL_{int,bile}$ and $CL_{int,met}$.

($PS_{u,efflux}$) across the sinusoidal membrane and subsequent biliary excretion ($CL_{int,bile}$) and/or metabolism ($CL_{int,met}$) ($CL_{int}=CL_{int,bile}+CL_{int,met}$) (Fig. 10). In this model, hepatic intrinsic clearance can be described by $PS\times(CL_{int}/PS_{u,efflux}+CL_{int})$. This is close to $PS_{u,influx}$ when $PS_{u,efflux}\ll CL_{int}$, or $PS_{u,influx}\times(CL_{int}/PS_{u,efflux})$ when $PS_{u,efflux}\gg CL_{int}$ (see Eq. (7) or Eq. (8)). Based on this model, the mass balance equations to express the drugs transported in and out of the each compartment can be described as follows:

$$V_{sys}\frac{dC_{sys}}{dt}=Q_H\cdot C_{inlet}-(CL_{NH}+Q_H)\cdot C_{sys}+f_u'\cdot CL_{open,1}\cdot C_{sys}' \tag{10}$$

$$V_{inlet}\frac{dC_{inlet}}{dt}=Q_H\cdot C_{sys}-(Q_H-f_u\cdot PS_{u,influx})\cdot C_{inlet}+f_u'\cdot CL_{open,1}\cdot C_{inlet}'+k_i\cdot X_i+f_H\cdot PS_{u,efflux}\cdot C_H \tag{11}$$

$$V_H\frac{dC_H}{dt}=f_u\cdot PS_{u,influx}\cdot C_{inlet}-f_H\cdot(PS_{u,efflux}+CL_{int,bile}+CL_{int,met}+CL_{lactone})\cdot C_H+f_H'\cdot CL_{open,2}\cdot C_H' \tag{12}$$

$$\frac{dX_a}{dt}=-k_a\cdot X_a+R\cdot CL_{int,bile}\cdot f_H\cdot C_H \tag{13}$$

$$\frac{dX_i}{dt}=k_a\cdot X_a-k_i\cdot X_i+f_i'\cdot CL_{open,3}\cdot\frac{X_i'}{V_i} \tag{14}$$

$$V_{sys}'\frac{dC_{sys}'}{dt}=Q_H\cdot C_{inlet}'-(CL_{NH}'+Q_H+f_u'\cdot CL_{open,1})\cdot C_{sys}' \tag{15}$$

$$V_{inlet}\frac{dC_{inlet}'}{dt}=Q_H\cdot C_{sys}'-(Q_H+f_u'\cdot PS_{u,influx}'+f_u'\cdot CL_{open,1})\cdot C_{inlet}'+k_i'\cdot X_i'+f_H'\cdot PS_{u,efflux}'\cdot C_H' \tag{16}$$

$$V_H\frac{dC_H'}{dt}=f_u'\cdot PS_{u,influx}'\cdot C_{inlet}'+f_H\cdot CL_{lactone}\cdot C_H-f_H'\cdot(CL_{open,2}+PS_{u,efflux}'+CL_{int,bile}+CL_{int,met}')\cdot C_H' \tag{17}$$

$$\frac{dX_a'}{dt}=-k_a'\cdot X_a'+R'\cdot CL_{int,bile}'\cdot f_H'\cdot C_H' \tag{18}$$

$$\frac{dX_i'}{dt}=k_a'\cdot X_a'-\left(k_i'+\frac{f_i'\cdot CL_{open,3}}{V_i}\right)\cdot X_i' \tag{19}$$

Table 10 shows the means of the parameters. Applying the Laplace transformation $(\tilde{f}(s)=\int_0^\infty e^{-st}\cdot F(t)dt)$ and $s\rightarrow 0$, the following equations are obtained.

$$Q_H\cdot AUC_{inlet}-(CL_{NH}+Q_H)\cdot AUC_{sys}+f_u'\cdot CL_{open,1}\cdot AUC_{sys}'=0 \tag{20}$$

$$Q_H\cdot AUC_{sys}-(Q_H+f_u\cdot PS_{u,influx})\cdot AUC_{inlet}+f_u'\cdot CL_{open,1}\cdot AUC_{inlet}'+k_i\cdot\int_0^\infty X_i dt+f_H\cdot PS_{u,efflux}\cdot AUC_H=0 \tag{21}$$

$$f_u \cdot PS_{u,influx} \cdot AUC_{inlet} - f_H \cdot (PS_{u,efflux} + CL_{int,bile} + CL_{int,met} + CL_{lactone}) \cdot AUC_H + f_H' \cdot CL_{open,2} \cdot AUC_H' = 0 \quad (22)$$

$$-k_a \cdot \int_0^\infty X_a dt + R \cdot CL_{int,bile} \cdot f_H \cdot AUC_H = -F_a \cdot D \quad (23)$$

$$k_a \cdot \int_0^\infty X_a dt - k_i \cdot \int_0^\infty X_i dt + \frac{f_i' \cdot CL_{open,3}}{V_i} \cdot \int_0^\infty X_i dt = 0 \quad (24)$$

$$Q_H \cdot AUC_{inlet}' - (CL_{NH}' + Q_H + f_u' \cdot CL_{open,1}) \cdot AUC_{sys}' = 0 \quad (25)$$

$$Q_H \cdot AUC_{sys}' - (Q_H + f_u' \cdot PS_{u,influx}' + f_u' \cdot CL_{open,1}) \cdot AUC_{inlet}' + k_i' \int_0^\infty X_i' dt + f_H' PS_{u,efflux}' \cdot AUC_H' = 0 \quad (26)$$

$$f_u' \cdot PS_{u,influx}' \cdot AUC_{inlet}' + f_H \cdot CL_{lactone} \cdot AUC_H - f_H' \cdot (CL_{open,2} + PS_{u,efflux}' + CL_{u,efflux}' + CL_{int,bile}' + CL_{int,met}') \cdot AUC_H' = 0 \quad (27)$$

$$-k_a' \cdot \int_0^\infty X_a' dt + R' \cdot CL_{int,bile}' \cdot f_H' \cdot AUC_H' = -F_a' \cdot D' \quad (28)$$

$$k_a' \cdot \int_0^\infty X_a' dt - \left(k_i' \cdot + \frac{f_i' \cdot CL_{open,3}}{V_i} \right) \cdot \int_0^\infty X_i' dt = 0 \quad (29)$$

where F_a is the fraction absorped in intestine, and D and D' are the dose of statins admininstered as open acid and lactone forms, respectively.

In the case of open acid statins, the ratio of the area under the time-unbound concentration of statins in the circulating blood curve (f_u*AUC_{sys}) to that under the time-unbound concentration of statins in the liver curve (f_H*AUC_H) can be described as follows:

$$\frac{f_u \cdot AUC_{sys}}{f_H \cdot AUC_H} = \frac{Q_H}{Q_H + CL_{NH}} \cdot \frac{PS_{u,efflux} + CL_{int,bile} + CL_{int,met} + CL_{lactone}}{PS_{u,influx}} - \frac{Q_H \cdot CL_{lactone}}{Q_H + CL_{NH}} \left[\left\{ \frac{f_u \cdot CL_{open,1} \left(\frac{CL_{open,2} + PS_{u,efflux}' + CL_{int,bile}' + CL_{int,met}'}{A} - 1 \right)}{CL_{NH}' + Q_H + f_u' \cdot CL_{open,1}} \right\} + \frac{1}{A} \cdot \frac{CL_{open,2}}{PS_{u,influx}} \right] \quad (30)$$

where,

$$A = CL_{open,2} + PS_{u,efflux}' + CL_{int,bile}' + CL_{int,met}' + \frac{f_u' \cdot PS_{u,efflux}' \cdot \left(\frac{R' \cdot CL_{int,bile}' \cdot K_i'}{k_i' + f_i' \cdot CL_{open,3}/V_i} + PS_{u,efflux}' \right)}{Q_H \cdot \left(\frac{Q_H}{Q_H + CL_{NH}' + f_u' \cdot CL_{open,1}} - \frac{Q_H + fu \, PS_{u,influx}' + fu' \cdot CL_{open,1}}{Q_H} \right)}$$

As this ratio of $f_u \cdot AUC_{sys}$ to $f_H \cdot AUC_H$ decreases, this means that the drug distributes to the liver specifically with low exposure to other tissues. Therefore, the drug with a lower ratio does not distribute to the target organ of the side effects but is highly exposed to the liver, suggesting a low likelihood of side effects with high pharmacological effects. In other words, this kind of statin has a wide therapeutic index with a wide safety margin. The reciprocal of the Eq. (30), that is, the ratio of $f_H \cdot AUC_H$ to $f_u \cdot AUC_{sys}$ reflects the width of the therapeutic index. When $CL_{lactone}$ is negligibly low, the reciprocal of the Eq. (30) gives the following equation:

$$\frac{f_H \cdot AUC_H}{f_u \cdot AUC_{sys}} = \frac{Q_H + CL_{NH}}{Q_H} \cdot \frac{PS_{u,influx}}{PS_{u,efflux} + CL_{int,bile} + CL_{int,met}} \quad (31)$$

As the extrahepatic clearance is negligible for all statins, this equation means that the safety margin of statins correlates with the ratio of the uptake of the statins by the liver ($PS_{u,influx}$) to the efflux, biliary excretion and metabolism ($PS_{u,efflux} + CL_{int,bile} + CL_{int,met}$). For a statin with a high hepatic uptake and low efflux, biliary excretion and metabolism will result in a marked pharmacological effect. Because the lactonization rate is, in fact, low as shown in Table 9, the safety margin is determined only

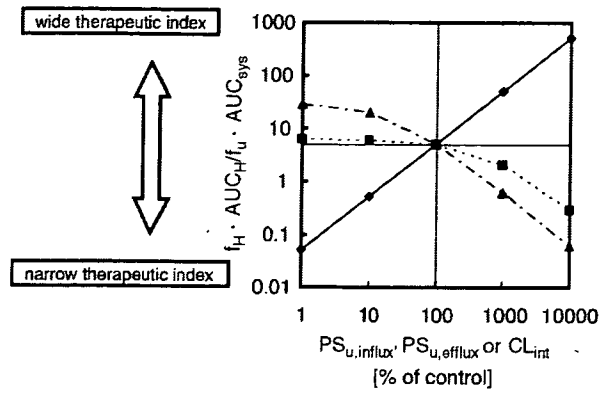

Fig. 11. Pharmacokinetic alterations associated with the change in $PS_{u,influx}$ (influx into hepatocytes), $PS_{u,efflux}$ (efflux from hepatocytes across the sinusoidal membrane) and CL_{int} (a hybrid parameter for biliary excretion and metabolism). The relationship between parameters ($PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int}) and $f_H \cdot AUC_H/f_u \cdot AUC_{sys}$ ratio. Simulated pharmacokinetc alterations caused by a change in $PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int} are shown. The $f_H \cdot AUC_H$ value represents the exposure of unbound statins to the liver, a target organ. A high $f_H \cdot AUC_H$ means a high pharmacological effect and a high $f_u \cdot AUC_{sys}$ may lead to exposure of unbound statins to other tissues and, therefore, a potential toxic side effect. Thus, a low $f_u \cdot AUC_{sys}$ with a high $f_H \cdot AUC_H$ means a selective distribution of statins to the liver, suggesting a high pharmacological effect with a low risk of side effects. Therefore, a statin with a high $f_H \cdot AUC_H/f_u \cdot AUC_{sys}$ ratio has a wide therapeutic index, with a high pharmacological effect and low likelihood of side effects.

by the balance of $PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int} ($=CL_{int,bile}+CL_{int,met}$). Fig. 11 shows the correlation between $PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int} and the ratio of $f_H \cdot AUC_H/f_u \cdot AUC_{sys}$. As shown in this figure, statins with a high $PS_{u,influx}$ and low $PS_{u,efflux}$ and CL_{int} are safe statins with a wide therapeutic index. A reduction in the $PS_{u,influx}$ caused by inter-individual differences in the transporter function or transporter-mediated drug–drug interactions will reduce the therapeutic index of statins.

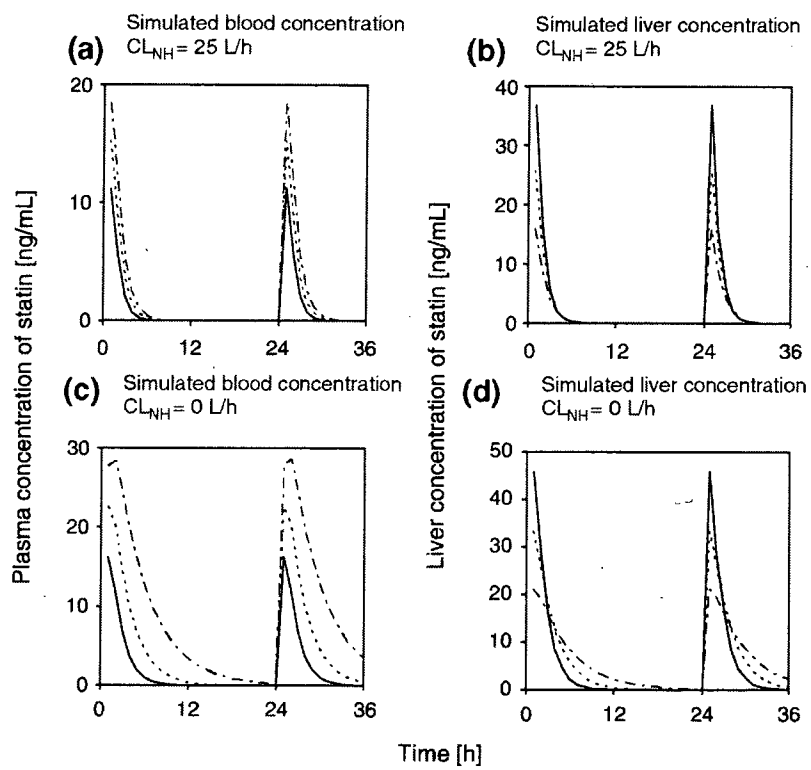

Fig. 12. Simulated blood and liver concentrations of statins for different $PS_{u,influx}$ values. The blood (**a**, **c**) and liver (**b**, **d**) concentrations of statin were simulated based on the physiologically based pharmacokinetic model shown in Fig. 9. (**a**, **b**) Simulation analysis shown by the solid line was performed using pravastatin parameters. Dotted and dashed lines show the simulated blood and liver concentrations of pravastatin when $PS_{u,influx}$ is reduced to 50% and 25% of the control, respectively (**c**, **d**). Similar simulation analyses were performed when the CL_{NH} was negligibly low. In this case, the area under the liver concentration–time curve is not altered by a change in $PS_{u,influx}$. However, the liver concentration–time profile is different when $PS_{u,influx}$ is reduced.

The AUC_H can be expressed by the following equation:

$$AUC_H = \frac{F_a \cdot D / \left\{ f_H \cdot \left(1 - \frac{f_u' \cdot CL_{spec,i}}{k_i \cdot V_i}\right)\right\}}{\left\{1 + \frac{Q_H \cdot CL_{int}}{f_u \cdot PS_{u,influx} \cdot (Q_H + CL_{int})}\right\} \cdot \left(PS_{u,efflux} + CL_{int,bile} + CL_{int,met} + CL_{int,other} - \frac{CL_{spec,i} \cdot CL_{int,bile}}{A}\right) + \frac{CL_{spec,i} \cdot CL_{int,bile}}{PS_{u,influx}} \left(1 - \frac{CL_{spec,i} + PS_{u,efflux} + CL_{int,bile} + CL_{int,met}}{A}\right) \cdot \left(1 - \frac{Q_H}{Q_H + CL_{int}} \cdot \frac{Q_H}{Q_H + CL_{int} \cdot f_u \cdot CL_{spec,i}}\right) - PS_{u,efflux} - \frac{f_u \cdot CL_{int,bile}}{1 - \frac{f_u' \cdot CL_{spec,i}}{k_i \cdot V_i}}} \quad (32)$$

This equation suggests that, for statins with an extrahepatic clearance (CL_{NH}) of 0 or close to zero, $f_H \cdot AUC_H$, that is, the exposure of statins to the liver, is not affected by $PS_{u,influx}$ hepatic uptake. This means that a reduction in $PS_{u,influx}$ does not affect the pharmacological effects of statins if there is a correlation between $f_H \cdot AUC_H$ and the pharmacological effect when CL_{NH} is negligibly low. Fig. 12 shows the plasma and liver concentrations of statins for different $PS_{u,influx}$ values. When $PS_{u,influx}$ decreases, that is, the hepatic uptake decreases, the plasma concentration increases. On the other hand, the liver concentration of statins falls for reduced $PS_{u,influx}$ values because of the reduced hepatic uptake. When $CL_{NH}=0$ or close to zero, the $f_H \cdot AUC_H$ is not altered for different $PS_{u,influx}$ values as described above (Fig. 12(**d**)). However, even in this case, the liver concentration–time profile appears to change with different $PS_{u,influx}$ values, leaving the $f_H \cdot AUC_H$ unchanged (Fig. 12(**d**)). If the pharmacological effect correlates with the $f_H \cdot AUC_H$, it would not change even if the $PS_{u,influx}$ was altered. However, if it was correlated with the liver concentration–time profile, then the pharmacological effect might be changed in the case of altered $PS_{u,influx}$ values because the maximum liver concentration and elimination rate from the liver is changed.

5. Clinically relevant drug–drug interactions with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

5.1. OATP1B1 inhibitor

Among OATP1B1 inhibitors, there are only a few drugs which may cause a drug–drug interaction with coadministered drugs in clinical situations because of the lower therapeutic concentrations compared with K_i (Shitara et al., 2005). Among them, cyclosporin A (CsA) is one of the drugs which may affect the pharmacokinetics of other drugs by the inhibition of OATP1B1-mediated hepatic uptake. In addition, CsA also affects CYP3A4 and P-gp as well as OATP1B1. CsA affects the plasma concentrations of simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin (Arnadottir et al., 1993; Regazzi et al., 1993; Goldberg & Roth, 1996; Olbricht et al., 1997; Muck et al., 1999; Asberg et al., 2001; Ichimaru et al., 2001; Park et al., 2001; Hasunuma et al., 2003; Simonson et al., 2004). The pharmacokinetic changes in these statins are shown in Table 11. Among them, the interactions with pravastatin, pitavastatin and rosuvastatin are possibly due to OATP1B1 inhibition because they are not substrates of CYP3A4 and P-gp. As far as the interaction with cerivastatin is concerned, it has been reported that CsA inhibits OATP1B1-mediated hepatic uptake but not P450-mediated metabolism at therapeutic concentrations, suggesting this interaction is caused by transporter-inhibition (Shitara et al., 2003). In fact, the plasma concentration of cerivastatin was increased in patients concomitantly taking CsA (Muck et al., 1999). The plasma concentration of cerivastatin with or without coadministration of CsA is shown in Fig. 13(**a**). It is notable that coadministration of CsA increased the AUC, in other words, it decreased the oral clearance but it did not change the elimination half life ($t_{1/2}$). It is quite different from the interaction with gemfibrozil, which is shown in Fig. 13(**b**). $t_{1/2}$ life can be described by using CL_{tot} and distribution volime (V_d) as following:

$$t_{1/2} = \ln 2 \cdot \frac{V_d}{CL_{tot}} \quad (33)$$

In the case of the interaction between cerivastatin and CsA, CsA decreased the hepatic uptake and clearance of cerivastatin. As cerivastatin is highly and selectively distributed to the liver via transporter-mediated hepatic uptake, decreased hepatic uptake by the inhibition of hepatic uptake transporter leads to the reduction in not only CL_{tot} but also V_d. Thus, CsA decreased the V_d and CL_{tot} values of cerivastatin equally at the same time, resulting in little change of $t_{1/2}$ (see Eq. (33)).

Schneck et al. reported that gemfibrozil altered the plasma concentration of rosuvastatin by the inhibition of its OATP1B1-mediated hepatic uptake (Schneck et al., 2004). They showed that gemfibrozil inhibited the OATP1B1-mediated uptake at the relatively lower concentration (i.e. $IC_{50}=4.0$ μM) using OATP1B1-expressing *Xenopus laevis* oocytes. On the other hand, our group has shown that gemfibrozil and its glucuronide may not inhibit the OATP1B1-mediated hepatic clearance of cerivastatin at therapeutic unbound concentrations (i.e. 0.65–1.0 and 2 μM for gemfibrozil and its glucuronide, respectively) with the IC_{50} values of 72 and 24 μM, respectively, using OATP1B1-expressing mammalian cells (Shitara et al., 2003). This discrepancy may be due to the difference in the experimental system. However, gemfibrozil actually altered the pharmacokinetics of rosuvastatin and pravastatin to a small extent although it did not alter that of pitavastatin (Kyrklund et al., 2003; Mathew et al., 2004; Schneck et al., 2004; Table 11). Thus, gemfibrozil or its metabolite may reduce the OATP1B1-mediated hepatic uptake to a small extent. In the case of the interaction between cerivastatin and