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Evidence for a role of human organic anion transporters in the muscular side effects of HMG-CoA reductase inhibitors

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Abstract

The purpose of this study was to elucidate the role of human organic anion transporters (human OATs) in the induction of drug-induced skeletal muscle abnormalities. 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors have been clinically used for lowering plasma cholesterol levels, and are known to induce various forms of skeletal muscle abnormalities including myopathy and rhabdomyolysis. Immunohistochemical analysis revealed that human OAT1 and human OAT3 are localized in the cytoplasmic membrane of the human skeletal muscles. The activities of human OATs were measured using mouse cell lines from renal proximal tubules stably expressing human OATs. Human OAT3, but not human OAT1, mediates the transport of pravastatin. Fluvastatin inhibited organic anion uptake mediated by human OAT1 in a mixture of competitive and noncompetitive manner, whereas simvastatin and fluvastatin noncompetitively inhibited the organic anion uptake mediated by human OAT3. In conclusion, the organic anion transporters OAT1 and OAT3 are localized in the cytoplasmic membrane of human skeletal muscles. Pravastatin, simvasatin, and fluvasatin inhibit human OATs activity. These results suggest that muscle organic anion transporters play a role in the muscular side effects of HMG-CoA reductase inhibitors.

Keywords: Organic anion transporter; Skeletal muscle; HMG-CoA reductase; Rhabdomyolysis; Transport

1. Introduction

The excretion of numerous organic anions, including endogenous metabolites, drugs, and xenobiotics, is an important physiological function of the kidney. Recently, cDNAs encoding the human organic anion transporters (human OATs) have been successively cloned, including human OAT1 (Reid et al., 1998; Hosoyamada et al., 1999), human OAT2 (Enomoto et al., 2002), human OAT3 (Cha et al., 2001), and human OAT4 (Cha et al., 2000). We have been elucidating the localization and functional roles of human OATs mainly in the kidney.

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is the rate-limiting step in cholesterol biosynthesis from acetate. The inhibition of this enzyme reduces cytoplasmic cholesterol levels in hepatocytes, which respond by increasing the synthesis of low-density lipoprotein (LDL) receptors that are expressed on hepatocyte surface membranes. This in turn increases hepatic LDL uptake from the plasma, reducing the plasma LDL concentration (Ritter et al., 1999). Thus, HMG-CoA reductase inhibitors have been used to lower plasma total and LDL levels in patients with hypercholesterolemia, which prevents the progression of atherosclerosis.

It has been recently shown that pravastatin, a HMG-CoA reductase inhibitor that possesses anionic moieties, is transported by rat OAT1 and rat OAT3 (Hasegawa et al., 2002). In addition to the kidney, mRNAs from human OATs were shown to be expressed in various organs including the brain, liver, skeletal muscles, and placenta (Hosoyamada et al., 1999; Cha et al., 2000, 2001). In the human skeletal muscles, HMG-CoA reductase inhibitors, including pravastatin, fluvastatin, and simvastatin (Fig. 1), were shown to induce various forms of skeletal muscle abnormalities ranging from mild myopathy to myositis, and occasionally rhabdomyolysis and even death (Evans and Rees, 2002). These lines of

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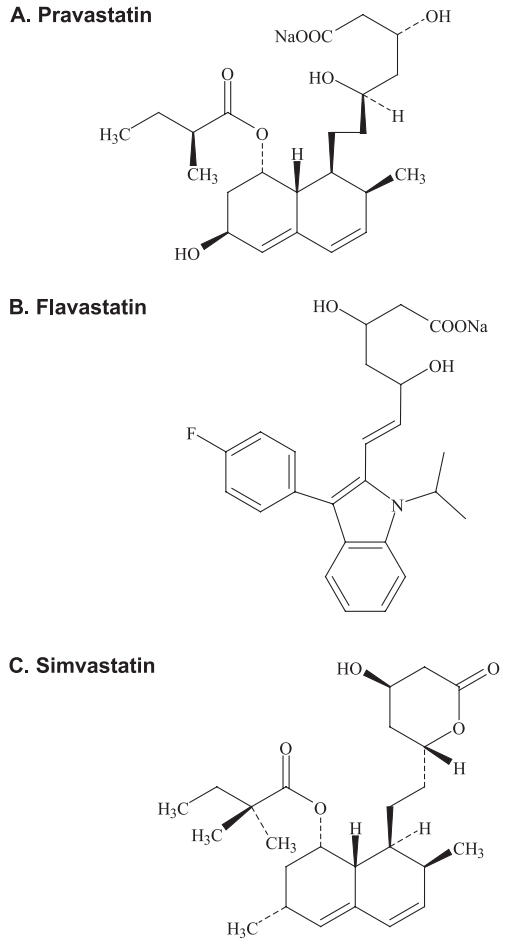

Fig. 1. Chemical structures of statins: (A) pravastatin, (B) fluvastatin, and (C) simvastatin.

evidence raise the possibility that human OAT1 and human OAT3 localized in the cytoplasmic membrane of the skeletal muscles mediate the uptake of HMG-CoA reductase inhibitors into the skeletal muscles and the induction of skeletal muscle abnormalities. In order to elucidate this hypothesis, firstly, we performed an immunohistochemical analysis of human OAT1 and human OAT3 in the human skeletal muscles. Secondly, we examined whether human OAT1 and human OAT3 mediate the transport of pravastatin. Thirdly, we elucidated the interactions of human OAT1 and human OAT3 with HMG-CoA reductase inhibitors, including fluvastatin and simvastatin. The activities of human OATs were measured using mouse cell lines from renal proximal tubules stably expressing human OATs.

2. Materials and methods

2.1. Materials

Adult human normal skeletal muscle tissue slides were purchased from Bio-chain (Hayward, CA, USA). The human skeletal muscle tissues were from a 26-year-old male. Other materials used included fetal bovine serum, trypsin, and geneticin from Invitrogen (Carlsbad, CA); recombinant epidermal growth factor from Wakunaga (Hiroshima, Japan); insulin from Shimizu (Shizuoka, Japan); RITC 80-7 culture medium from Iwaki (Tokyo, Japan); and simvastatin from Wako (Tokyo, Japan). [^{14}C]pravastatin and fluvastatin were kind gifts from Sankyo Pharmaceutical (Tokyo, Japan) and Novartis Pharm (Tokyo, Japan), respectively.

2.2. Immunohistochemical analysis of human OAT1 and human OAT3 in human skeletal muscle tissues

The generation of antibodies against human OAT1 and human OAT3 was already described previously (Hosoyamada et al., 1999; Cha et al., 2001). Light microscopic analysis of human OAT1 and human OAT3 was performed as previously described (Tojo et al., 1999). Briefly, wax-embedded sections (2 μm) were cut and stained by the labeled streptavidin–biotin method. After dewaxing, the sections were incubated with 3% H_2O_2 for 15 min and then with blocking serum for 15 min. The sections were then incubated with polyclonal antibodies against human OAT1 and human OAT3 (1:100 dilution) for 2 h. The section incubated with Tris-buffered saline with 0.1% Tween 20 served as negative control. The sections were rinsed with Tris-buffered saline containing 0.1% Tween 20 and incubated with the biotinylated secondary antibody against rabbit immunoglobulin (Dako, Glostrup, Denmark) for 1 h. After rinsing with Tris-buffered saline containing 0.1% Tween 20, the sections were incubated for 30 min with horseradish peroxidase-conjugated streptavidin solution. Horseradish peroxidase labeling was detected using a peroxidase substrate solution with diaminobenzidine (0.8 mM; Dojindo Laboratories, Kumamoto, Japan). The sections were then counterstained with hematoxylin before examination under a light microscope.

2.3. Cell culture

The establishment and characterization of the second segment of the proximal tubule (S_2) cells stably expressing human OAT1 and human OAT3 (S_2 human OAT1 and S_2 human OAT3) were performed as previously reported by us (Khamdang et al., 2002). These cells were grown in a humidified incubator at 33 °C and under 5% CO_2 using the RITC 80-7 medium containing 5% fetal bovine serum, 10 mg/ml transferrin, 0.08 U/ml insulin, 10 ng/ml recombinant epidermal growth factor, and 400 μg/ml geneticin. The cells were subcultured for 25–35 passages in a medium containing 0.05% trypsin–EDTA solution (containing, in mM: 137 NaCl, 5.4 KCl, 5.5 glucose, 4 $NaHCO_3$, 0.5 EDTA, and 5 HEPES; pH 7.2).

2.4. Uptake experiments

Uptake experiments were performed as previously described (Enomoto et al., 2002; Khamdang et al., 2002). The S_2 cells were seeded in 24-well tissue culture plates at a density of 1×10^5 cells/well. After the cells were cultured for 2 days, the cells were washed three times with Dulbecco's modified phosphate-buffered saline solution (containing, in mM: 137 NaCl, 3 KCl, 8 $NaHPO_4$, 1 KH_2PO_4, 1 $CaCl_2$, and 0.5 $MgCl_2$, pH 7.4) and then preincubated in the same solution in a water bath at 37 °C for 10 min. The cells were then incubated in a solution containing 25 μM [^{14}C]pravastatin at 37 °C for 2 min. The uptake was terminated by adding ice-cold Dulbecco's modified phosphate-buffered saline, and the cells were washed three times with the same solution. The cells in each well were lysed with 0.5 ml of 0.1 N sodium hydroxide and 2.5 ml of aquasol-2, and radioactivity was determined using a β-scintillation counter (LSC-3100; Aloka, Tokyo, Japan).

2.5. Inhibition study

After preincubation as described above, S_2 human OAT1 and S_2 human OAT3 were incubated in a solution containing either 5 μM [^{14}C]para-aminohippuric acid (human OAT1) or 50 nM [^{3}H]estrone sulfate (human OAT3) in the absence or presence of various concentrations of fluvastatin or simvastatin at 37 °C for 2 min. Uptake experiments were performed as described above.

2.6. Kinetic analysis

After preincubation as described above, S_2 human OAT1 and S_2 human OAT3 were incubated in a solution containing various concentrations of either [^{14}C]*para*-aminohippuric acid (human OAT1) or [^{3}H]estrone sulfate (human OAT3) at 37 °C for 2 min in the absence or presence of fluvastatin at 50 μM (human OAT1) and 10 μM (human OAT3), or simvastatin at 50 μM (human OAT3). Because simvastatin could not be solubilized in a solution at a concentration more than 100 μM, it was impossible for us to determine the mode of inhibitory effect of simvastatin on human OAT1. Based on the organic anion uptake under each condition, double reciprocal plot analyses were performed as previously described (Enomoto et al., 2002).

2.7. Statistical analyses

Data are expressed as means ± S.E. Statistical differences were determined using one-way analysis of variance with Dunnett's post-hoc test. Differences were considered significant at $P < 0.05$.

3. Results

3.1. Immunolocalization of human OAT1 and human OAT3 in human skeletal muscles

As shown in Fig. 2, human OAT1 (A) and human OAT3 (B) were stained in the cytoplasmic membrane of the skeletal

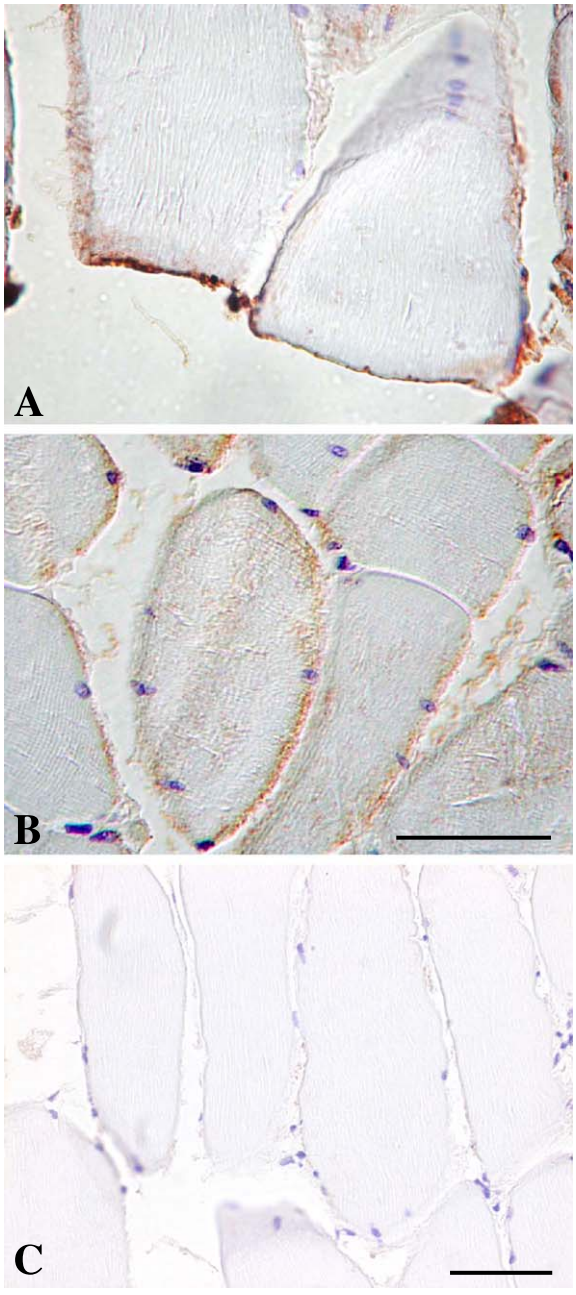

Fig. 2. Light microscopy illustrating immunohistochemistry for human OAT1 and human OAT3 in human skeletal muscles. Human skeletal muscle tissues were stained with polyclonal antibodies against human OAT1 (A) and human OAT3 (B). Original magnification × 380 in (A) and (B). There was no staining in the negative control without primary antibody (C). The bar indicates 50 μm.

muscles, but the muscle fibers were not stained. The negative control exhibited no immunoreactivity (C).

3.2. Pravastatin uptake mediated by human OAT1 and human OAT3

We examined whether human OAT1 and human OAT3 mediate the uptake of pravastatin. As shown in Fig. 3, human OAT3, but not human OAT1, exhibited significantly higher uptake activities of pravastatin than mock cells ($n=8$, $^{*}P<0.001$ vs. mock).

3.3. Effects of fluvastatin and simvastatin on organic anion uptake mediated by human OAT1 and human OAT3

We examined the inhibitory effects of various concentrations of fluvastatin and simvastatin on organic anion uptake mediated by human OAT1 and human OAT3. As shown in Fig. 4, fluvastatin as well as simvastatin dose-dependently inhibited organic anion uptake mediated by human OAT1 (A, B) and human OAT3 (C, D) ($n=4$, $^{*}P<0.05$, $^{**}P<0.01$, and $^{***}P<0.001$ vs. control). Table 1 shows the IC_{50} values of fluvastatin and simvastatin for the organic anion uptake mediated by human OAT1 and human OAT3.

3.4. Kinetic analysis of effects of fluvastatin and simvastatin on organic anion uptake mediated by human OATs

In order to further elucidate the inhibitory effects of fluvastatin and simvastatin on organic anion uptake mediated by human OAT1 and human OAT3, we performed the analyses of Lineweaver–Burk plots. As shown in Fig. 5A, lines of the Lineweaver–Burk plots for the inhibitory effect of fluvastatin on human OAT1 intersect in the second quadrant, corresponding to the mixed type inhibition. On the other hand, lines of the Lineweaver–Burk plots for the inhibitory effects of fluvastatin and simvastatin on human OAT3 intersect with the horizontal axis,

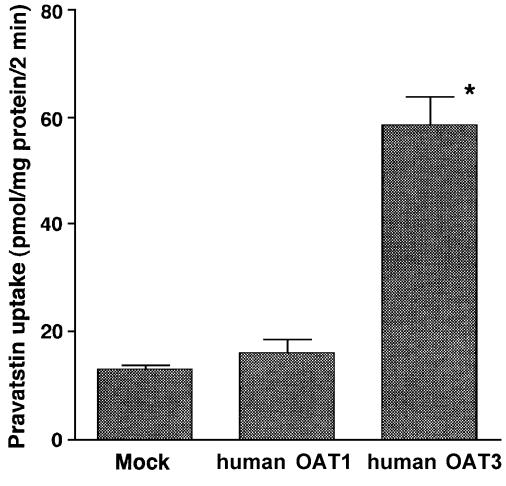

Fig. 3. Pravastatin uptake mediated by human OAT1 and human OAT3. S_2 human OAT1, S_2 human OAT3, and mock were incubated in a solution containing 25 μM [^{14}C]pravastatin for 2 min at 37 °C. Each value represents the mean ± S.E. of eight monolayers from two separate experiments ($^{*}P<0.001$ vs. mock).

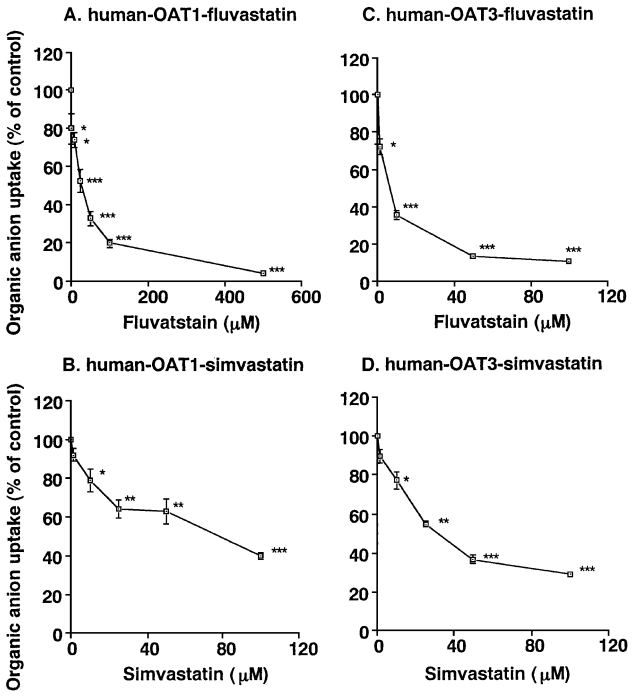

Fig. 4. Effects of various concentrations of fluvastatin and simvastatin on organic anion uptake mediated by human OAT1 and human OAT3. S_2 human OAT1 and S_2 human OAT3 were incubated in solution containing either 5 μM [^{14}C]*para*-aminohippuric acid (human OAT1) or 50 nM [^{3}H]estrone sulfate (human OAT3) in the presence of various concentrations of fluvastatin and simvastatin at 37 °C for 2 min. (A) Human OAT1–fluvastatin, (B) human OAT1–simvastatin, (C) human OAT3–fluvastatin, and (D) human OAT3–simvastatin. Each value represents the mean ± S.E. of four monolayers from one typical experiment of two separate experiments ($^{*}P<0.05$, $^{**}P<0.01$, and $^{***}P<0.001$ vs. control).

Table 1
IC_{50} values of HMG-CoA reductase inhibitors for the organic anion uptake mediated by human OAT1 and human OAT3

	IC_{50} (μM)		Therapeutically relevant plasma concentration of drug (μM)
	Human OAT1	Human OAT3	
Fluvastatin	26.3 ± 4.63	5.79 ± 0.64	2.30
Simvastatin	73.6 ± 6.60	32.3 ± 1.57	0.55
Pravastatin	408 ± 54.5[a]	13.7 ± 0.61[a]	0.43

S_2 human OAT1 and S_2 human OAT3 were incubated in solution containing either 5 μM [^{14}C]*para*-aminohippuric acid (human OAT1) or 50 nM [^{3}H]estrone sulfate (human OAT3) in the presence of various concentrations of fluvastatin and simvastatin at 37 °C for 2 min. Each value represents the mean ± S.E. of six monolayers from two separate experiments.

Plasma concentrations of HMG-CoA reductase inhibitors have been derived from the works of Hardman and Limbird (2001). Therapeutically relevant plasma concentrations of drugs are defined as fivefold of steady-state maximal plasma concentrations of drugs (Zhang et al., 2000).

[a] Unpublished observation.

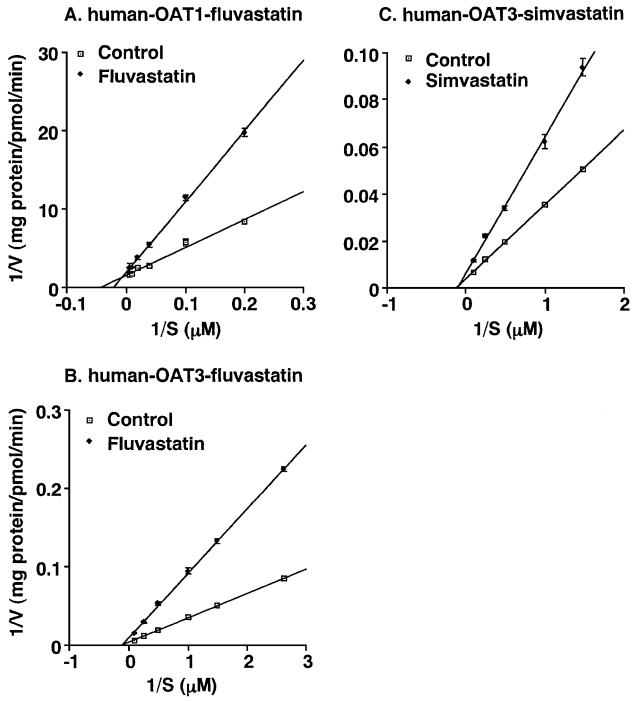

Fig. 5. Kinetic analyses of the effects of fluvastatin and simvastatin on organic anion uptake mediated by human OAT1 and human OAT3. S_2 human OAT1 and S_2 human OAT3 were incubated in solution containing various concentrations of either [^{14}C]*para*-aminohippuric acid (human OAT1) or [^{3}H]estrone sulfate (human OAT3) in the absence or presence of fluvastatin at 10 μM for human OAT1 and 50 μM for human OAT3, or simvastatin at 50 μM for human OAT3 at 37 °C for 2 min. Analyses of Lineweaver–Burk plots were performed. (A) Human OAT1–fluvastatin, (B) human OAT3–fluvastatin, and (C) human OAT3–simvastatin. Control shows S_2 human OAT1 or S_2 human OAT3 cells treated with vehicle. Each value represents the mean ± S.E. of four monolayers from one typical experiment of two separate experiments.

corresponding to the noncompetitive type inhibition (Fig. 5B and C).

4. Discussion

Among adverse drug reactions by HMG-CoA reductase inhibitors, skeletal muscle abnormalities and hepatotoxicity are the most clinically important (Omar et al., 2001). Increases of creatine kinase concentrations to more than three times the upper limit of normal have been reported in 3–5% of patients (Omar et al., 2001; Stalenhoef et al., 1989; Ziegler and Drouin, 1990). Skeletal muscle abnormalities can range from benign myalgia to myopathy, which is defined as a 10-fold elevation of the creatine kinase concentration (Herman, 1999). When HMG-CoA reductase inhibitors are prescribed as monotherapy, the incidence of myopathy is approximately 0.1–0.5% and is dose-related (Maron et al., 2000; Garnett, 1995). If myopathy is not recognized and HMG-CoA reductase inhibitors therapy is continued, necrosis of muscle cells and subsequent myoglobinuria may occur (Omar et al., 2001). This may result in life-threatening rhabdomyolysis. The incidence of rhabdodmyolysis when HMG-CoA reductase inhibitors are used alone has been reported to be 0.04–0.2% (Berland et al., 1991). The interaction of HMG-CoA reductase inhibitors with drugs that are metabolized via common pathways increases the risk of myopathy and rhabdomyolysis up to 10-fold (Herman, 1999).

In the current study, immunohistochemical analysis revealed that human OAT1 and human OAT3 were localized to the cytoplasm membrane of the skeletal muscles. In addition, human OAT3, but not human OAT1, mediated the transport of pravastatin. The result is consistent with the fact that the IC_{50} value of pravastatin for human OAT3 was approximately 30-fold lower than that for human OAT1, as shown in Table 1. The result is in contrast to that using rat OATs, where rat OAT1 as well as rat OAT3 mediate the uptake of pravastatin (Hasegawa et al., 2002), suggesting the interspecies difference of the functional property of OAT1 between humans and rats. Thus, it was suggested that human OAT3 is associated with the uptake of pravastatin into the skeletal muscles and the subsequent induction of skeletal muscle abnormalities.

Since the transport of substrates consists of three processes (i.e., substrate binding, translocation, and dissociation), the inhibitory effects of fluvastatin and simvastatin on human OAT1 and human OAT3 do not necessarily indicate that these substrates are transported by human OAT1 and human OAT3. In this regard, uptake experiments of fluvastatin and simvastatin should be performed. However, it is possible that these HMG-CoA reductase inhibitors are taken up into skeletal muscles mediated by human OAT1 and human OAT3, which leads to the induction of skeletal muscle abnormalities. In addition, as shown in Table 1, the therapeutically relevant plasma concentrations of fluvastatin, simvastatin, and pravastatin were approximately 2.5-, 60-, and 30-fold lower than the IC_{50} values of these HMG-CoA reductase inhibitors for human OAT3, and were approximately 10-, 130-, and 900-fold lower than those for human OAT1. Thus, it is possible that human OATs mediate the transport of HMG-CoA reductase inhibitors in vivo, whereas the rate of transport is slow.

The incidence of rhabdomyolysis per million prescriptions of pravastatin, simvastatin, and fluvastatin was reported to be 0.04, 0.12, and 0, respectively (Staffa et al., 2002). The rank order of this incidence was not correlated with that of the IC_{50} values of HMG-CoA reductase inhibitors for human OAT1 and human OAT3 (Table 1). For example, although the IC_{50} values of fluvastatin for human OAT1 and human OAT3 were the lowest among the HMG-CoA reductase inhibitors tested in the present study, the incidence of rhabdomyolysis by fluvastatin was the lowest (i.e., 0). The possible reason for this discrepancy is that all HMG-CoA reductase inhibitors, except pravastatin, are lypophilic; thus, they can be distributed into the tissues by passive diffusion, in addition to a specific pathway including human OATs or the involvement of transporters other than human OAT1 and

human OAT3 in the uptake of drugs and the subsequent induction of skeletal muscle abnormalities.

We have already demonstrated that human OAT1 and human OAT3 mediate the transport of nonsteroidal anti-inflammatory drugs including salicylate and ibuprofen (Khamdang et al., 2002), and these drugs were reported to induce rhabdomyolysis (Ross and Hoppel, 1987; Leventhal et al., 1989). Thus, considering the localization of human OAT1 and human OAT3 in the skeletal muscles, it is possible that human OAT1 and human OAT3 mediate the distribution of nonsteroidal anti-inflammatory drugs into the skeletal muscles, potentially resulting in the induction of various forms of skeletal muscle abnormalities.

The urinary excretion rates of unchanged pravastatin, fluvastatin, and simvastatin were reported to be 2–6%, 0.34%, and negligible, respectively (Sasahara et al., 1988; Dain et al., 1993; Hardman and Limbird, 2001). In this regard, human OAT3 was shown to be localized to the basolateral side of the proximal tubule (Cha et al., 2001). Thus, it was suggested that human OAT3 is associated with basolateral uptake of pravastatin, which is the first step of tubular secretion of pravastatin.

In conclusion, the organic anion transporters OAT1 and OAT3 are localized in the cytoplasmic membrane of human skeletal muscles. Pravastatin, simvasatin, and fluvasatin inhibit human OATs activity. These results suggest that muscle organic anion transporters play a role in the muscular side effects of HMG-CoA reductase inhibitors.

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