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Human organic cation transporter 3 mediates the transport of antiarrhythmic drugs

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Abstract

Antiarrhythmic drugs have been considered to be transported by the organic cation transport system. The purpose of this study was to elucidate the molecular mechanism underlying the transport of antiarrhythmic drugs using cells from the second segment of the proximal tubule (S_2) cells of mice expressing human-organic cation transporter 3 (S_2 human-OCT3). The antiarrhythmic drugs tested were cibenzoline, disopyramide, lidocaine, mexiletine, phenytoin, pilsicanide, procainamide and quinidine. Human-OCT3 mediated a time- and dose-dependent uptake of quinidine and lidocaine, with K_m values of 216 and 139 μM, respectively. Human-OCT3 also mediated the uptake of disopyramide and procainamide but not that of phenytoin. All antiarrhythmic drugs tested inhibited histamine uptake mediated by human-OCT3 in a dose-dependent manner. The IC_{50} values of antiarrhythmic drugs for human-OCT3 ranged between 0.75 and 656 μM. Kinetic analysis revealed that disopyramide, lidocaine, procainamide and quinidine inhibited histamine uptake mediated by human-OCT3 in a competitive manner. In conclusion, these results suggest that human-OCT3 mediates the transport of antiarrhythmic drugs, which may be the mechanism underlying the distribution and the elimination of these drugs.

Keywords: Antiarrhythmic drug; Organic cation transporter; Transport; Quinidine; Lidocaine

1. Introduction

The transepithelial transport of organic cations plays an important role in the elimination of xenobiotics from the body by the liver and kidney (Pritchard and Miller, 1993). In the liver, numerous organic cations, including endogenous metabolites, drugs and xenobiotics, are removed from the circulation. This clearance process is achieved via the basolateral transport system, which mediates the hepatocellular uptake of organic cations. In the kidney, the secretion of organic cations is an important physiological function of the renal proximal tubule. The process of secreting organic cations through the proximal tubule cells is achieved via unidirectional transcellular transport involving the uptake of organic cations from blood across the basolateral membrane into the cells, followed by extrusion across the brush-border membrane into the proximal tubule fluid.

Functional studies led to the identification of two distinct classes of organic cation transport systems, one driven by the transmembrane potential difference and another driven by the transmembrane H^+ gradient (Kekuda et al., 1998). Recently, cDNAs encoding the human organic cation

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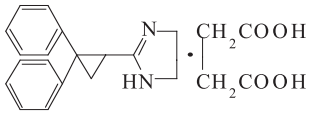
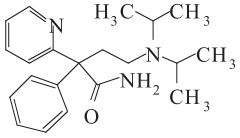
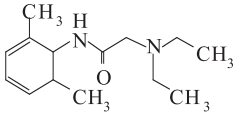
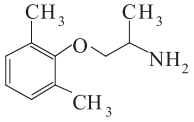
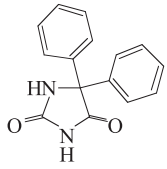
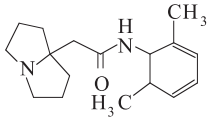
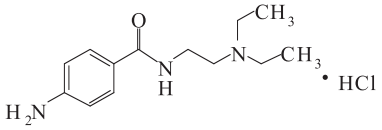
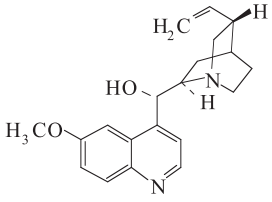
transporters (human-OCTs) have been successively cloned including human-OCT1 (Gorboulev et al., 1997), human-OCT2 (Gorboulev et al., 1997), human-OCT2-A (Urakami et al., 2002) and human-OCT3 (Wu et al., 2000). Human-OCT1, human-OCT2A and human-OCT3 mRNAs were shown to be expressed in the liver, whereas human-OCT2, human-OCT2A and human-OCT3 mRNA were expressed in the kidney (Gorboulev et al., 1997; Urakami et al., 2002; Wu et al., 2000).

Pharmacokinetically, as indicated by the urinary excretion rates of unchanged drugs shown in Table 1, antiarrhythmic drugs are eliminated by the liver as well as the kidney. Almost all of the antiarrhythmic drugs possess cationic moieties, and the organic cation transport systems have been considered to play an important role in the pharmacokinetic handling of antiarrhythmic drugs. However, it remains unclarified whether OCTs including human-OCT3 mediate the transport of antiarrhythmic drugs.

The purpose of this study was to elucidate the molecular mechanism underlying the transport of antiarrhythmic drugs using cells from the second segment of the proximal tubule (S_2) cells of mice expressing human-

Table 1
Structures, urinary excretion rates of unchanged forms of antiarrhythmic drugs and IC_{50} values for human-OCT3

Drugs	Structures	Urinary excretion rates of unchanged drugs (%)	IC_{50} values (μM)
Cibenzoline		55-62[1)]	128 ± 9.38
Disopyramide		55[3)]	457 ± 36.2
Lidocaine		2[3)]	656 ± 89.2
Mexiletine		4-15[3)]	266 ± 43.2
Phenytoin		2[3)]	0.75 ± 0.07
Pilsicanide		75-86[2)]	66.2 ± 7.32
Procainamide		67[3)]	355 ± 62.8
Quinidine		18[3)]	124 ± 19.8

1) From Terakawa et al. (1988), 2) from Nakajima et al. (1989) and 3) from Hardman and Limbird (2001). S_2 human-OCT3 cells were incubated in a solution containing 200 nM [^{3}H] histamine in the absence or presence of various concentrations of antiarrhythmic drugs for 1 min. Each value represents the mean±S.E. of eight monolayers from two separate experiments.

OCT3 (S_2 human-OCT3). The antiarrhythmic drugs tested in the current study are listed in Table 1.

2. Materials and methods

2.1. Materials

[^{3}H]histamine (458.8 GBq/mmol), [^{14}C]lidocaine (20.0 GBq/mmol) and [^{14}C]phenytoin (1.827 GBq/mmol) were purchased from Perkin Elmer Life Sciences (Boston, MA). [^{3}H]quinidine (740 GBq/mmol) was purchased from Muromachi Chemicals (Tokyo, Japan). Antiarrhythmic drugs, namely, disopyramide, lidocaine, mexiletine, phenytoin, procainamide and quinidine were, obtained from Sigma (St. Louis, MO). Cibenzoline and pilsicanide were kind gifts from Fujisawa (Osaka, Japan) and Daiichi (Tokyo, Japan), respectively. 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), the RITC 80-7 culture medium from Iwaki (Tokyo, Japan) and TfX-50 from Promega (Madison, WI).

2.2. Cell culture

S_2 cells were established by culturing the microdissected S_2 segment derived from transgenic mice harboring the temperature-sensitive simian virus 40 large T-antigen gene. S_2 human-OCT3 cells were established as previously described (Takeda et al., 2001). Briefly, the full-length cDNA of human-OCT3 was synthesized by annealing oligonucleotides obtained from Takara (Shiga, Japan) on the basis of the cDNA sequence published by Wieland et al. (2000). The full-length cDNA of human-OCT3 was subcloned into pcDNA 3.1 (Invitrogen), a mammalian expression vector. S_2 human-OCT3 cells were obtained by transfecting S_2 cells with pcDNA 3.1-human-OCT3, using TfX-50 according to the manufacturer's instructions. S_2 cells transfected with pcDNA 3.1 lacking an insert were designated as S_2 pcDNA 3.1 (mock) and used as control. 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 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) for 25–35 passages. Clonal cells were isolated using a cloning cylinder and screened by determining the optimal substrate for human-OCT3, that is, [^{3}H]histamine (Grundemann et al., 1999). S_2 human-OCT3 exhibited a time- and dose-dependent uptake of [^{3}H]histamine and [^{3}H]1-methyl-4-phenylpyridinium (MPP) with K_m values of 219 and 38.8 μM, respectively, which were consistent with previous studies, that is, 180 and 47 μM, respectively (Grundemann et al., 1999; Wu et al., 2000). In addition, longitudinal sections of S_2 human-OCT3 cells, stained with polyclonal antibodies against human-OCT3, showed that the subcellular localization of human-OCT3 proteins was mainly on the cell membrane. Both the basolateral and apical portions of the membrane exhibited positive staining. Therefore, the cells were cultured on a solid support in these experiments.

2.3. Uptake experiments

Uptake experiments were performed as previously described (Takeda et al., 2001). 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 (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 various substrates at 37 °C. The concentrations of substrates were 500 μM for cibenzoline, 1000 μM for disopyramide, 5 μM for lidocaine, 5 μM for phenytoin, 1000 μM for procainamide and 200 nM for quinidine. The uptake of radiolabelled substrates was stopped 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 0.1N sodium hydroxide and 2.5 ml of aquasol-2, and radioactivity was determined using a β-scintillation counter (LSC-3100, Aloka, Tokyo, Japan). The intracellular concentration of disopyramide was determined by enzyme immunoassay using an EMIT disopyramide assay kit (Dade Behring, Tokyo, Japan), whereas that of procainamide was determined by fluorescence polarization immunoassay using a Abbott TDX kit (Abbott Japan, Tokyo, Japan).

2.4. Inhibition study

To evaluate the inhibitory effects of antiarrhythmic drugs on histamine uptake mediated by human-OCT3, S_2 human-OCT3 cells were incubated in a solution containing [^{3}H]histamine for 1 min in the absence or presence of various concentrations of antiarrhythmic drugs at 37 °C. S_2 human-OCT3 exhibited a time-dependent uptake of histamine up to 2 min (data not shown). Disopyramide, lidocaine, mexiletine, pilsicanide and procainamide were dissolved in H_2O, whereas cibenzoline, phenytoin and quinidine were dissolved in dimethyl sulfoxide and diluted with the incubation medium. The final concentration of dimethyl sulfoxide in the incubation medium was adjusted to less than 0.2%. The amount

of histamine uptake in S_2 human-OCT3 cells for 1 min was approximately fivefold higher than that in mock cells.

2.5. Kinetic analysis of inhibition

After preincubation as described above, S_2 human-OCT3 cells were incubated in a solution containing [^{3}H]histamine at various concentrations in the absence or presence of either disopyramide at 1000 μM, lidocaine at 1000 μM, procainamide at 1000 μM or quinidine at 250 μM at 37 °C for 1 min. Analyses of Lineweaver–Burk plots were performed as previously described by us (Takeda et al., 2001).

2.6. Statistical analysis

Data are expressed as means±S.E. Statistical differences were determined using one-way analysis of variance with Dunnett's post hoc test or Student's *t*-test. Differences were considered significant at $P<0.05$.

3. Results

3.1. Quinidine and lidocaine uptake by human-OCT3

We have elucidated whether human-OCT3 mediates the uptake of quinidine. Human-OCT3 exhibited a time-dependent uptake of quinidine up to 15 min. In order to further elucidate the property of quinidine transport mediated by human-OCT3, we performed kinetic analysis of quinidine uptake. Human-OCT3 mediated a dose-dependent uptake of quinidine (Fig. 1A), and the Eadie–Hofstee analysis revealed that the K_m value for human-OCT3-mediated quinidine uptake was 216±23.4 μM.

We have also elucidated whether human-OCT3 mediates the uptake of lidocaine. Human-OCT3 mediated a time-dependent uptake of lidocaine up to 5 min. In order to further elucidate the property of lidocaine transport mediated by human-OCT3, we performed kinetic analysis of lidocaine uptake. Human-OCT3 mediated a dose-dependent uptake of lidocaine (Fig. 1B), and the Eadie–Hofstee analysis revealed that the K_m value for human-OCT3-mediated lidocaine uptake was 139±27.3 μM.

3.2. Uptake of disopyramide, phenytoin and procainamide mediated by human-OCT3

We have also elucidated whether human-OCT3 mediates the uptake of disopyramide, phenytoin and procainamide. As shown in Fig. 2, S_2 human-OCT3 exhibited significantly higher uptake activities of disopyramide (A) and procainamide (C) than mock, but not that of phenytoin (B). These results suggest that human-OCT3 mediates the transport of disopyramide and procainamide, but not phenytoin.

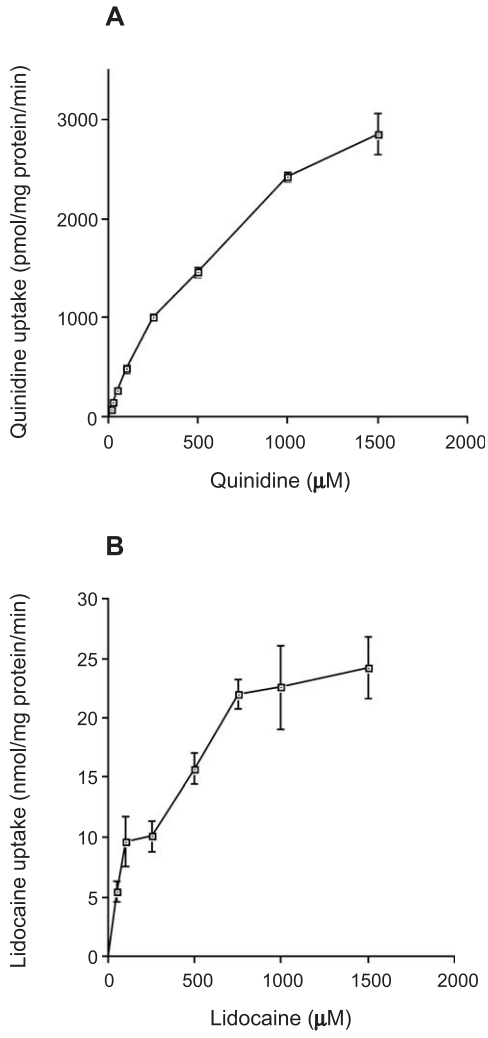


Fig. 1. Quinidine and lidocaine uptake by human-OCT3. (A) S_2 human-OCT3 and mock cells were incubated in a solution containing [^{3}H]quinidine at various concentrations at 37 °C for 5 min. (B) S_2 human-OCT3 and mock cells were incubated in a solution containing [^{3}H]lidocaine at various concentrations at 37 °C for 2 min. Each value represents the mean±S.E. of eight monolayers from two separate experiments.

3.3. Effects of antiarrhythmic drugs on histamine uptake mediated by human-OCT3

We have examined the inhibitory effects of various concentrations of antiarrhythmic drugs on histamine uptake mediated by human-OCT3. As shown in Fig. 3, disopyramide (A), lidocaine (B), procainamide (C) and quinidine (D) inhibited histamine uptake mediated by human-OCT3 in a dose-dependent manner. Similarly, other antiarrhythmic drugs, namely, cibenzoline, mexiletine, phenytoin and pilsicanide, inhibited histamine uptake mediated by human-OCT3 in a dose-dependent manner (data not shown). The IC_{50} values are listed in Table 1.

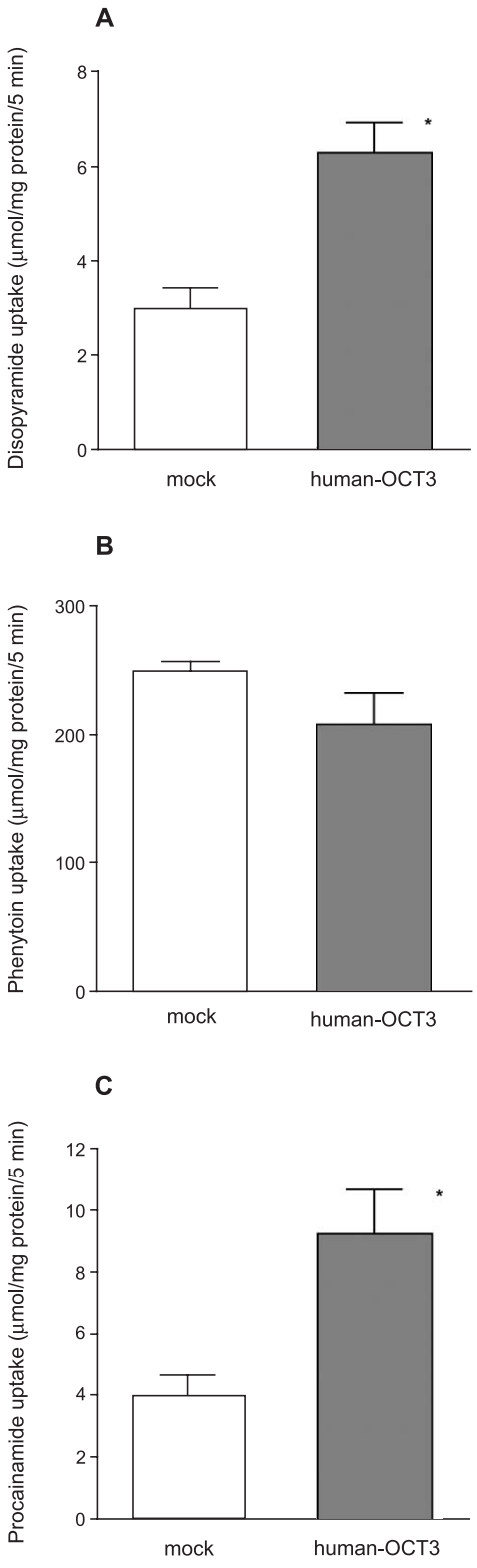


Fig. 2. Uptake of disopyramide, phenytoin and procainamide by human-OCT3. S_2 human-OCT3 and mock cells were incubated in a solution containing 1000 μM disopyramide (A), 5 μM [^{3}H]phenytoin (B) or 1000 μM procainamide (C) at 37 °C for 5 min. The intracellular concentration of disopyramide was determined by enzyme immunoassay, whereas that of procainamide was determined by fluorescence polarization immunoassay. Each value represents the mean±S.E. of eight monolayers from two separate experiments. *P<0.01 vs. mock.

In order to further elucidate the inhibitory effects of disopyramide, lidocaine, procainamide and quinidine on histamine uptake mediated by human-OCT3, we performed kinetic analyses of these inhibitory effects. Disopyramide, lidocaine, procainamide and quinidine competitively inhibited histamine uptake mediated by human-OCT3 (data not shown).

4. Discussion

In 1998, rat-OCT3 cDNA was isolated from placenta (Kekuda et al., 1998). Subsequent studies revealed that rat-OCT3 is identical to the extraneuronal monoamine transporter that has been described functionally as a transporter specific for monoamines (Wu et al., 1998). Human-OCT3 cDNA has been cloned from human placenta and revealed to be a potential-sensitive organic cation transporter (Grundemann et al., 1999; Wu et al., 2000). Human-OCT3 was shown to mediate the transport of various cationic substrates including tetraethylammonium, MPP, guanidine, dopamine, norepinephrine and histamine. Because S_2 human-OCT3 exhibited transport properties comparable with those previously reported (Grundemann et al., 1999; Wu et al., 2000), we attempted to elucidate the interactions of human-OCT3 with antiarrhythmic drugs using the S_2 cell line.

Human-OCT3 mediated the transport of antiarrhythmic drugs, namely, disopyramide, lidocaine, procainamide and quinidine. Various studies of the effects of antiarrhythmic drugs on organic cation uptake by OCTs have been performed (Grundemann et al., 1994; Gorboulev et al., 1997; Zhang et al., 1998; Okuda et al., 1999; Wu et al., 2000; Arndt et al., 2001; Kakehi et al., 2002). However, to the best of our knowledge, this is the first demonstration of OCTs mediating the transport of antiarrhythmic drugs.

As indicated by the urinary excretion rates of unchanged drugs shown in Table 1, antiarrhythmic drugs are eliminated by the liver and the kidney. It was reported that human-OCT3 mRNA is expressed in the human liver and human kidney as determined by Northern blot analysis (Wu et al., 2000). Real-time polymerase chain reaction analysis also revealed that human-OCT3 mRNA is expressed in the human kidney (Motohashi et al., 2002). In situ hybridization study revealed that mouse-OCT3 is seen in the proximal and distal convoluted tubules (Wu et al., 2000). Although the precise localization of human-OCT3 within the liver and the kidney remains unknown, it was suggested that the transport of antiarrhythmic drugs by human-OCT3 is associated with the pharmacokinetic handling of these drugs in the liver and the kidney.

It was speculated that OCT3 plays a major role in the barrier function of the placenta, protecting the developing fetus from possible deleterious effects of endobiotics produced by the fetus, as well as xenobiotics that may be present in the maternal circulation (Leazer and Klaassen,

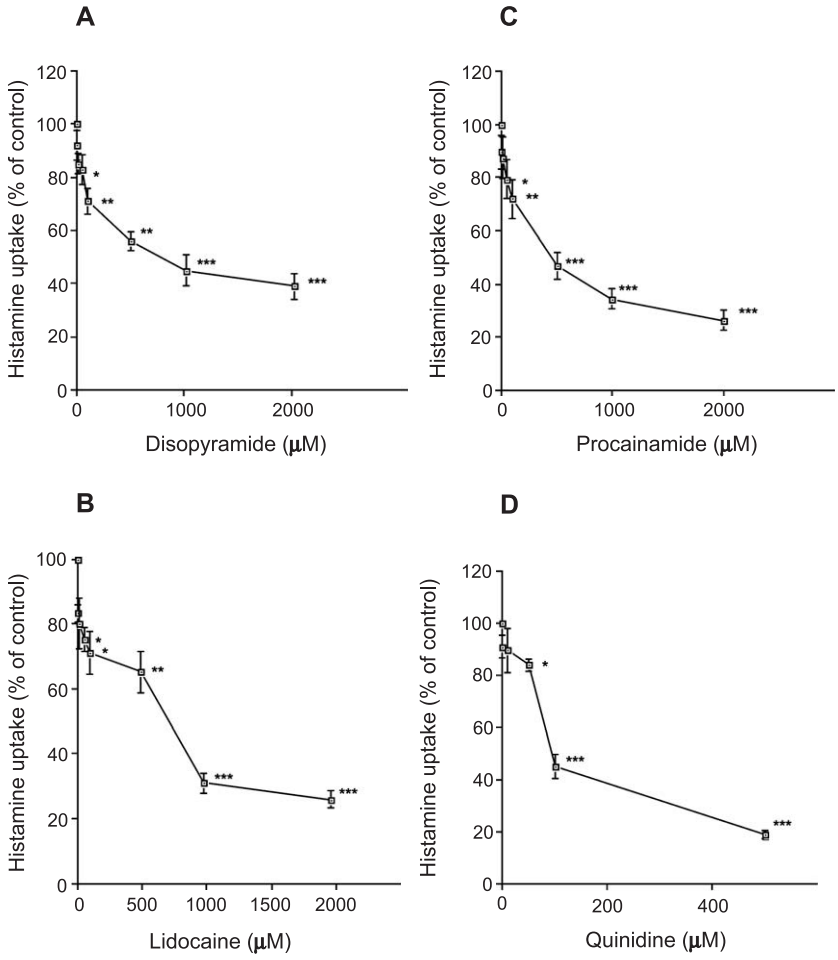


Fig. 3. Effects of various concentrations of antiarrhythmic drugs on histamine uptake mediated by human-OCT3. S_2 human-OCT3 cells were incubated in a solution containing 200 nM [^{3}H]histamine for 1 min in the absence or presence of various concentrations of disopyramide (A), lidocaine (B), procainamide (C) or quinidine (D) at 37 °C. Each value represents the mean±S.E. of eight monolayers from two separate experiments. *P<0.05, **P<0.01 and ***P<0.001 vs. control.

2003). Human-OCT3 mRNA was highly expressed in the placenta (Wu et al., 2000). In addition, we found that human-OCT3 mediates the transport of antiarrhythmic drugs. Based on these findings, it is possible that human-OCT3 is a pathway of antiarrhythmic drugs between mother and fetus. Teratogenicity and other serious side effects induced by antiarrhythmic drugs have not been reported yet except that phenytoin induces a teratogenicity such as the neuroblastoma induction (Sherman and Roizen, 1976) or an adverse drug reaction such as a bleeding tendency (Hey, 1999). However, because the safeness of antiarrhythmic drugs during pregnancy has not been established yet, it is considered that these drugs can be administered during pregnancy only when the advantage of administration overweighs the risk of the drugs.

Central nervous system side effects were of antiarrhythmic drugs including lidocaine and quinidine (Dorian, 2000). Clinical manifestations of these side effects are drowsiness and confusion caused by lidocaine and cinchonism by quinidine. Human-OCT3 mRNA is also expressed in the brain (Wu et al., 2000). In situ hybridization showed that rat-OCT3 mRNA is expressed in different brain regions, particularly in the hippocampus, cerebellum and cerebral cortex (Wu et al., 1998). In addition, Shang et al. (2003) reported that cerebellar granule neurons in rats express human-OCT3, which mediates the uptake of MPP. Furthermore, we found that human-OCT3 mediates the transport of lidocaine and quinidine. According to these findings, it is possible that human-OCT3 is associated with the induction of adverse drug reactions in the central nervous system by lidocaine and quinidine.

To predict whether human-OCT3 mediates the transport of antiarrhythmic drugs in vivo, K_m or IC_{50} value and free plasma concentration were compared among antiarrhythmic drugs. The free plasma concentrations of disopyramide, lidocaine, procainamide and quinidine were calculated to be 3.08, 6.39, 6.80 and 3.08 μM, respectively (Hardman and Limbird, 2001). These values were approximately 150-, 100-, 50- and 70-fold higher than the K_m or IC_{50} values of disopyramide, lidocaine, procainamide and quinidine for human-OCT3, respectively. Although the K_m or IC_{50} values were much higher than the free plasma

concentrations of antiarrhythmic drugs, we have speculated that human-OCT3 mediates the transport of disopyramide, lidocaine, procainamide and quinidine in vivo, for the following reason. Wang et al. (2002) have demonstrated that rats infused with metformin exhibit a plasma metformin concentration of 3.03 μM. The protein-binding rate of metformin was reported to be negligible (Hardman and Limbird, 2001). Wang et al. (2002) have also reported that the K_m value of metformin for rat-OCT1 is 377 μM. Although, the K_m value of metformin for OCT1 was approximately 100-fold higher than the free plasma concentration of metformin, it was demonstrated that OCT1 mediates the uptake of metformin in the liver using OCT1 gene-knockout mice (Wang et al., 2002). Thus, it was predicted that human-OCT3 mediates the transport of quinidine, lidocaine and disopyramide in vivo, although its speed of transport is slow.

In conclusion, human-OCT3 mediated the transport of antiarrhythmic drugs, namely, quinidine, lidocaine, disopyramide and procainamide, which may be the molecular mechanism underlying the elimination and the distribution of these drugs in various organs.

Acknowledgements

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