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Full Paper

Interactions of Organic Anion Transporters and Organic Cation Transporters With Mycotoxins

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Abstract. Mycotoxins are secondary metabolites of moulds that which exert adverse effects in humans and animals. It is known that direct cellular toxicity is often associated with increased cellular accumulation of toxic compounds, and membrane transport may be the first fundamental stage in the development of the cytotoxicity. To elucidate the entry pathway for mycotoxins into cells, we have investigated the interactions of human and rat organic anion transporters (hOATs/rOats) and human organic cation transporters (hOCTs) with mycotoxins using cells stably expressing hOATs/rOats/hOCTs. The mycotoxins tested were aflatoxin B1, α-zearalenol, citrinin, citrioveridine, cyclopiazonic acid, fumonisin B1, gliotoxin, patulin, penicillic acid, rubratoxin B, and zearalenone. These mycotoxins inhibited organic anion uptake mediated by hOAT1-4, and organic cation uptake mediated by hOCT1-2. By comparing the IC_{50} values of mycotoxins for hOATs, it was found that hOAT1 and hOAT3 exhibited higher affinity interactions with mycotoxins than hOAT2 and hOAT4. There was no interspecies difference between humans and rats for the interactions of OATs with mycotoxins except that of OAT3 with rubratoxin B. Finally, we observed that hOAT1-4 and hOCT1-2 mediated the uptake of aflatoxin B1. In conclusion, hOATs and hOCTs interacted with various mycotoxins. Considering the localization of hOATs/rOats and hOCTs, it was suggested that these transporters were the possible entrance pathway for mycotoxins in kidney and liver, leading to the induction of adverse effects in humans and rats.

Keywords: organic anion transporter, organic cation transporter, SLC22, mycotoxin, aflatoxin

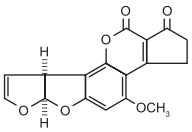
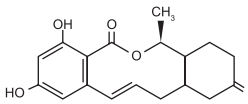
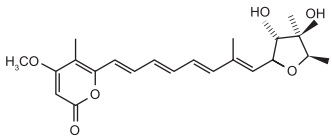
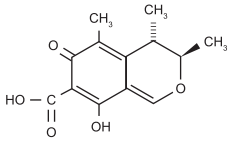
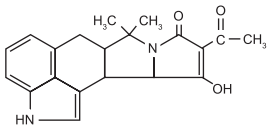
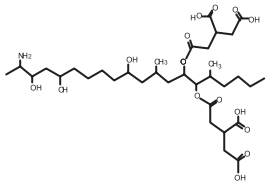
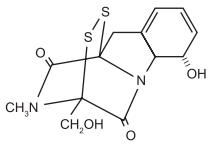
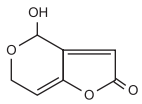
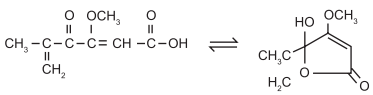
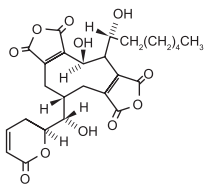
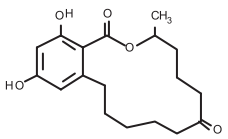
Introduction

Mycotoxins, chemicals produced by moulds, may have developed to serve as a chemical defense system against insects, microorganisms, nematodes, grazing animals, and humans (1). Among approximately 300 known mycotoxins, some of them are capable of producing the disease "mycotoxicosis" and death in humans and animals. Although mycotoxicosis occurs more frequently in areas with a hot and humid climate, which is favorable for the growth of moulds, they can also be found in temperate zones. Exposure to mycotoxins may occur through ingestion, inhalation, and dermal contact. Massive mycotoxin contamination of food resulting in outbreaks of diseases is only a rare occurence today in developing countries. The primary concern is the long-term effects of ingesting food contaminated with low levels of mycotoxins.

From the structural point of view, mycotoxins are classified into a diverse group of organic compounds of low molecular weight, which range from a single heterocyclic ring of 50 Da to groups of irregularly arranged 6- or 8-membered rings with molecular weight greater than 500 Da. Among the toxic effects of mycotoxins, hepatic and renal insufficiencies are the most commonly described effect of acute mycotoxin poisoning. Some mycotoxins act primarily by interfering with protein synthesis after permeating the plasma

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Table 1. Mycotoxins tested in this study

Names	Chemical structures	Molecular weight
Aflatoxin B		312.3
α-Zearalenol		320.4
Citreoviridin		402.5
Citrinin		250.3
Cyclopiazonic acid		336.4
Fumonisin B1		721.8
Gliotoxin		326.4
Patulin		154.1
Penicillic acid		170.2
Rubratoxin		518.5
Zearalanone		318.4

membrane (2). For the entry of these hydrophilic compounds, special membrane proteins such as transporters are required, because they cannot penetrate the lipid bilayer of the cell membrane.

The secretion of numerous organic anions and cations, including endogenous metabolites, drugs, and xenobiotics, is an important physiological function of kidneys and liver (3). In the kidneys, the process of secreting organic anions and cations through the proximal tubular cells is achieved via unidirectional transcellular transport involving the uptake of organic anions and cations into the cells from the blood across the basolateral membrane, followed by extrusion across the brush-border membrane into the tubular lumen (4). cDNAs encoding the human organic anion transporter (hOAT) family have been successively cloned, including OAT1 to OAT4 (5, 6). The human organic cation transporters (hOCTs) isolated thus far are OCT1 to OCT3 (7). The roles of OATs and OCTs in the pharmacokinetics of drugs have been gradually clarified not only in the kidney, but also in other organs including the liver (8).

Although the elucidation of the molecular mechanisms of the plasma membrane permeation of mycotoxins is important to understand the development of their cytotoxicity, studies have mainly focused on ochratoxin A so far (9 – 13). In order to elucidate the entry pathway for various mycotoxins into the cells, we have first demostrated the interactions of hOATs and hOCTs with mycotoxins using proximal tubular cells stably expressing hOAT1, hOAT2, hOAT3, hOAT4, hOCT1, and hOCT2 (S2 hOAT1, S2 hOAT2, S2 hOAT3, S2 hOAT4, S2 hOCT1, and S2 hOCT2). In addition, the species difference between human and rat for the interactions of OATs with mycotoxins was elucidated using S2 hOAT1/Oat1 and S2 hOAT3/Oat3. The mycotoxins tested in the current study are listed in Table 1.

Materials and Methods

Materials

[^{14}C]*para*-Aminohippuric acid (PAH) (1.86 GBq /mmol), [^{3}H]prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (6808 GBq /mmol), [^{3}H]estrone sulfate (ES) (1961 GBq/mmol), and [^{14}C]tetraethylammonium (TEA) (2.035 GBq/mmol) were purchased from Perkin Elmer Life Sciences (Boston, MA, USA). [^{3}H]Aflatoxin B1 (25 GBq/mmol) was purchased from Muromachi Chemicals (Tokyo). Mycotoxins were obtained from Sigma Chemical Co. (St. Louis, MO, USA). Other materials used included fetal bovine serum, trypsin, and geneticin from Invitrogen (Carlsbad, CA, USA), recombinant epidermal growth factor from Wakunaga (Hiroshima), insulin from Shimizu (Shizuoka), RITC 80-7 culture medium from Iwaki Co. (Tokyo), and TfX-50 from Promega (Madison, WI, USA).

Cell culture

S2 cells were established by culturing the microdissected S2 segment derived from transgenic mice harboring the temperature-sensitive simian virus 40 large T-antigen gene as described previously (14). S2 is the segment of the proximal tubule where hOAT1 and hOAT3 are localized (15, 16). The establishment and characterization of S2 hOAT1, S2 hOAT2, S2 hOAT3, S2 hOAT4, S2 hOCT1, and S2 hOCT2 and S2 cells stably expressing rat Oat1 and rat Oat3 (S2 rOat1 and S2 rOat3) were reported previously (17). These cells were grown in a humidified incubator at 33°C and under 5% CO_2 using 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 mg/ml geneticin. The cells were subcultured in a medium containing 0.05% trypsin-EDTA solution (137 mM NaCl, 5.4 mM KCl, 5.5 mM glucose, 4 mM $NaHCO_3$, 0.5 mM EDTA, and 5 mM Hepes, pH 7.2) and used for 25 – 35 passages. Clonal cells were isolated using a cloning cylinder and screened by determining the optimal substrate for each transporter, that is, [^{14}C]PAH for hOAT1 and rOat1; [^{3}H]$PGF_{2\alpha}$ for hOAT2; [^{3}H]ES for hOAT3, rOat3, and hOAT4; and [^{3}H]TEA for hOCT1 and hOCT2. These compounds are recognized as prototypical transport substrates for these transporters as described previously (15, 16, 18 – 22).

Uptake experiments

Uptake experiments were performed as previously described (13). Cells were seeded in 24-well tissue culture plates at a density of 1×10^5 cells/well. After the cells were cultured for two days, the cells were washed three times with Dulbecco's modified phosphate-buffered saline (137 mM NaCl, 3 mM KCl, 8 mM $NaHPO_4$, 1 mM KH_2PO_4, 1 mM $CaCl_2$, and 0.5 mM $MgCl_2$, pH 7.4) supplemented with 5.5 mM glucose 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 100 nM [^{3}H]aflatoxin B1 at 37°C up to 30 min. The uptake was stopped by the addition of 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 by using a β-scintillation counter (LSC-3100; Aloka, Tokyo).

Inhibition study

To evaluate the inhibitory effects of mycotoxins on organic anion uptake mediated by hOAT1, hOAT2, hOAT3, hOAT4, rOat1, and rOat3 and organic cation uptake mediated by hOCT1 and hOCT2, the cells were incubated in a solution containing either [^{14}C]PAH for 2 min (hOAT1 and rOat1), [^{3}H]$PGF_{2\alpha}$ for 20 s (hOAT2), [^{3}H]ES for 2 min (hOAT3, rOat3 and hOAT4), or [^{3}H]TEA for 5 min (hOCT1 and hOCT2) in the absence or presence of various concentrations of mycotoxins at 37°C. Dose-dependent inhibition experiments were performed at concentrations up to 1 mM, whereas the interaction of hOAT2 with aflatoxin B1 was examined at concentrations up to 2 mM. We have already confirmed that the concentrations of the compounds up to 2 mM did not have any cytotoxic effect within 1 h (data not shown). All of the mycotoxins tested were dissolved in dimethylsulfoxide and diluted with the incubation medium. The final concentration of dimethylsulfoxide in the incubation medium was adjusted to less than 0.4 %.

Statistical analysis

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

Results

Effects of mycotoxins on organic anion uptake mediated by hOATs

We examined the inhibitory effects of various concentrations of mycotoxins on the organic anion uptake mediated by hOAT1, hOAT2, hOAT3, and hOAT4. Figure 1 shows the effects of aflatoxin B1 on the organic anion uptake mediated by hOAT1, hOAT2, hOAT3, and hOAT4. Aflatoxin B1 significantly inhibited the organic anion uptake mediated by hOAT1 (A), hOAT2 (B), hOAT3 (C), and hOAT4 (D) in a dose-dependent manner. Similarly, other mycotoxins including α-zearalenol, citrioverdine, citrinin, cyclopiazonic acid, fumonisin B1, gliotoxin, patulin, penicillic acid, and zearalenone significantly inhibited the organic anion uptake mediated by hOAT1, hOAT2, hOAT3, and hOAT4, whereas no inhibition was observed for hOAT2 with fumonisin B1, gliotoxin, patulin, penicillic acid, and rubratoxin B, hOAT3 with rubratoxin B, and hOAT4 with rubratoxin B. The IC_{50} values of aflatoxin B1, α-zearalenol, citrioveridine, cyclopiazonic acid, fumonisin B1, gliotoxin, patulin, and zearalenone for the organic anion uptake by hOATs are listed in Table 2, and the effects of citrinin, penicillic acid, and rubratoxin B at 1 mM on the organic anion uptake by hOATs are listed in Table 3.

Comparison of effects of mycotoxins on organic anion uptake mediated by OATs between humans and rats

In order to elucidate whether there are any interspecies differences for the interactions of OAT1 and OAT3 with mycotoxins between humans and rats, we examined the effects of various mycotoxins (1 mM) on the organic anion uptake mediated by hOAT1, hOAT3, rOat1, and rOat3. As shown in Fig. 2, mycotoxins at 1 mM significantly inhibited the organic anion uptake mediated by rOat1 and hOAT1 (A) and rOat3 and hOAT3 (B), with the exception of the effect of rubratoxin B on hOAT3.

Effects of mycotoxins on organic cation uptake mediated by hOCTs

We also examined the effects of various concentrations of mycotoxins on the organic cation uptake mediated by hOCT1 and hOCT2. As shown in Fig. 1, aflatoxin B1 significantly inhibited TEA uptake mediated by hOCT1 (E) and hOCT2 (F). Similarly, other mycotoxins including α-zearalenol, citrioveridine, citrinin, cyclopiazonic acid, fumonisin B1, gliotoxin, patulin, penicillic acid, rubratoxin B, and zearalenone significantly inhibited the organic cation uptake mediated by hOCT1 and hOCT2, whereas no inhibition was observed for hOCT1 with patulin, penicillic acid, and rubratoxin B and for hOCT2 with citrinin, fumonisin B1, and penicillic acid. The IC_{50} values of aflatoxin B1, α-zearalenol, citrioveridine, cyclopiazonic acid, fumonisin B1, gliotoxin, patulin, and zearalenone for the organic cation uptake by hOCTs are listed in Table 2; and the effects of citrinin, penicillic acid, and rubratoxin B at 1 mM on the organic cation uptake by hOCTs are listed in Table 3.

Aflatoxin B1 uptake mediated by hOATs and hOCTs

In order to determine whether hOATs and hOCTs mediate the uptake of mycotoxins, we evaluated the uptake activities of [^{3}H]aflatoxin B1, which is commercially available in Japan, by hOATs and hOCTs. The uptake rates of [^{3}H]aflatoxin B1 by hOAT1, hOAT2, hOAT3, hOAT4, hOCT1, and hOCT2 were significantly higher than that by mock (Fig. 3). These results suggest that hOAT1, hOAT2, hOAT3, hOAT4, hOCT1, and hOCT2 mediate the transport of aflatoxin B1.

Discussion

The transport characteristics of OATs and OCTs and their localization have been elucidated mainly in the kidneys and liver. These transporters mainly mediate

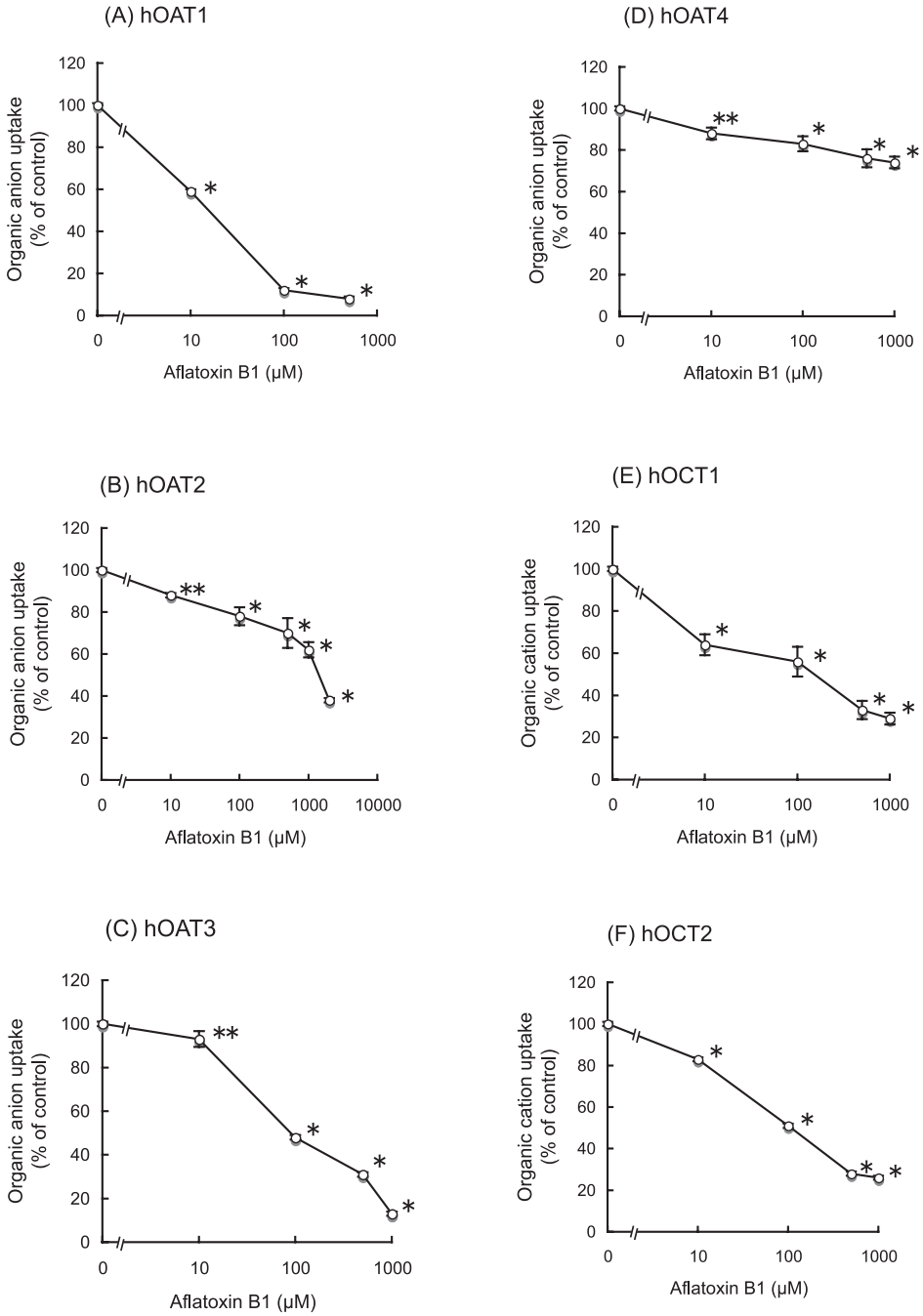


Fig. 1. Effects of various concentrations of aflatoxin B1 on the organic anion uptake mediated by hOATs and the organic cation uptake mediated by hOCTs. S2 hOAT1 (A), S2 hOAT2 (B), S2 hOAT3 (C), S2 hOAT4 (D), S2 hOCT1 (D), and S2 hOCT2 (E) were incubated in solution containing 5 μM [^{14}C]PAH (hOAT1), 50 nM [^{3}H]PGF$_{2\alpha}$ (hOAT2), 50 nM [^{3}H]ES (hOAT3 and hOAT4), or 5 μM [^{14}C]TEA in the presence of various concentrations of aflatoxin B1 at 37°C for 2 min (hOAT1, hOAT3, and hOAT4), 20 s (hOAT2), or 5 min (hOCT1 and hOCT2). Each value represents the mean ± S.E.M. of six monolayers from two separate experiments. *P<0.001 and **P<0.01 *vs* control.

the transport of organic ions with a molecular weight <500 (3). As a consequence of the secretory roles for xenobiotics, kidneys and liver are exposed to several toxicants including small organic compounds mycotoxins (50 – 500 Da). The most commonly described effects of acute mycotoxin poisoning are hepatic and renal insufficiencies, which may lead to death in extreme cases. It is known that direct cellular toxicity is often associated with increased cellular accumulation of toxic compounds. Thus, transport via OATs and OCTs may be

Table 2. IC_{50} values of mycotoxins for organic anion uptake by hOATs and organic cation uptake by hOCTs

Mycotoxin	hOAT1	hOAT2	hOAT3	hOAT4	hOCT1	hOCT2
			(μM)			
Aflatoxin B1	12.3	1502	13.1	>1000	64.4	121
α-Zearalenol	28.4	180	4.55	130	1.70	34.3
Citreoverdine	16.9	>1000	6.63	823	6.63	17.7
Cyclopiazonic acid	6.59	126	1.90	86.6	>1000	>1000
Fumonisin B1	768		181	>1000	>1000	
Gliotoxin	117		73.9	>1000	584	117
Patulin	44.8		>1000	>1000		>1000
Zearalenone	147	149	6.71	103	0.62	24.8

S2 hOAT1, S2 hOAT2, S2 hOAT3, S2 hOAT4, S2 hOCT1, and S2 hOCT2 were incubated in a solution containing either 5 μM [^{14}C]PAH (hOAT1), 50 nM [^{3}H] $PGF_{2\alpha}$ (hOAT2), 50 nM [^{3}H]ES (hOAT3 and hOAT4), or 5 μM [^{14}C]TEA (hOCT1, hOCT2) in the absence or presence of various concentrations of mycotoxins for either 2 min (hOAT1, HOAT3, and hOAT4), 20 s (hOAT2), or 5 min (hOCT1 and hOCT2). Each value represents the mean of six monolayers from two separate experiments.

Table 3. Effects of citrinin, penicillic acid, and rubratoxin B at 1 mM on the organic anion uptake by hOATs and the organic cation uptake by hOCTs

Mycotoxin	Citrinin	Penicillic acid	Rubratoxin B
		(% of control)	
hOAT1	3.62 ± 0.07*	18.3 ± 2.51*	32.4 ± 2.58*
hOAT2	66.0 ± 2.59*	123 ± 4.76**	97.2 ± 2.27
hOAT3	14.5 ± 0.95*	43.6 ± 0.84*	100 ± 3.22
hOAT4	35.3 ± 1.24*	86.4 ± 2.03**	107 ± 3.77
hOCT1	16.5 ± 1.33*	88.4 ± 3.93	97.6 ± 7.12
hOCT2	114 ± 7.72***	112 ± 1.93***	65.7 ± 2.42*

S2 hOAT1, S2 hOAT2, S2 hOAT3, S2 hOAT4, S2 hOCT1, and S2 hOCT2 were incubated in a solution containing either 5 μM [^{14}C]PAH (hOAT1), 50 nM [^{3}H] $PGF_{2\alpha}$ (hOAT2), 50 nM [^{3}H]ES (hOAT3 and hOAT4), or 5 μM [^{14}C]TEA (hOCT1, hOCT2) in the absence or presence of citrinin, penicillic acid, and rubratoxin B at 1 mM for either 2 min (hOAT1, hOAT3, and hOAT4), 20 s (hOAT2), or 5 min (hOCT1 and hOCT2). Each value represents the mean S.E.M. of six monolayers from two separate experiments. *P<0.001, **P<0.01, and ***P<0.05 *vs* control.

the first fundamental stage in the development of nephro- and hapatotoxicity. To elucidate the entry pathway for mycotoxins into the cells, we have investigated the interactions of OATs and OCTs with mycotoxins using cells stably expressing hOATs/rOats/hOCTs in this study.

Mycotoxins such as aflatoxin B1, α-zearalenol, citrinin, citrioveridine, cyclopiazonic acid, fumonisin B1, gliotoxin, patulin, penicillic acid, rubratoxin B, and zearalenone (154.1 – 721.8 Da) inhibited organic anion uptake mediated by hOAT1-4 and organic cation uptake mediated by hOCT1-2. These results suggest that the mycotoxins tested here are the potential transport substrates for OATs and OCTs. Using the radiolabelled aflatoxin B1, which is the only commercially available mycotoxin in Japan besides ochratoxin A, we confirmed that hOAT1-4 and hOCT1-2 mediated the uptake of aflatoxin B1. Thus, OATs and OCTs are the potential entrance pathway for mycotoxins in kidneys and liver, leading to their intracellular accumulation.

By comparing the IC_{50} values of mycotoxins among hOATs, we found that hOAT1 and hOAT3 generally exhibit the highest affinity for mycotoxins, whereas hOAT2 and hOAT4 exhibit the lowest affinity for mycotoxins. This tendency was also true for the interactions of hOATs with ochratoxin A (12, 13), non-steroidal anti-inflammatory drugs (23), and organic anion transport inhibitors (24, 25). Thus, the affinity rank order for the interactions of hOATs with mycotoxins may not to be specific to mycotoxins, but may be applied in general. On the other hand, comparing the IC_{50} values of mycotoxins between hOCT1 and hOCT2, a significant difference (more than threefold difference) in the IC_{50} values was observed for α-zearalenol,

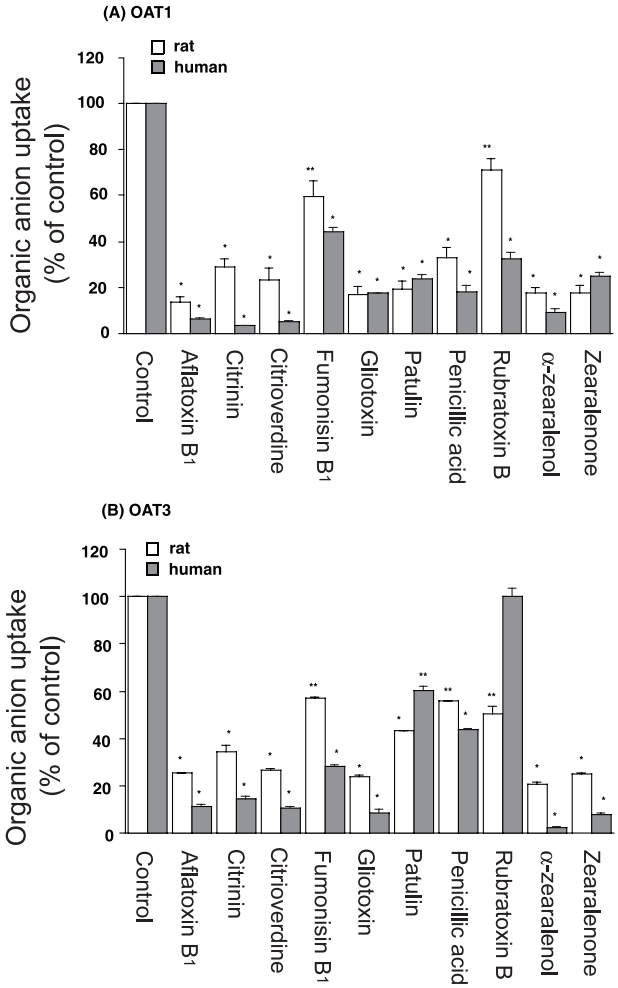


Fig. 2. Comparison of the effects of various mycotoxins on the organic anion uptake mediated by OAT1 and OAT3 between humans and rats. S2 hOAT1, S2 rOat1, S2 hOAT3, and S2 rOat3 were incubated in solution containing 5 μM [^{14}C]PAH (hOAT1 and rOAT1) or 50 nM [^{3}H]ES (hOAT3 and rOAT3) in the presence of various mycotoxins at 1 mM at 37°C for 2 min. (A) OAT1 and (B) OAT3. Each value represents the mean ± S.E.M. of six monolayers from two separate experiments. **P*<0.001 and ***P*<0.01 *vs* control.

gliotoxin, and zearalenone. Applying the same criteria, a previous report suggests that hOCT1 and hOCT2 are distinct for the interactions with progesterone, β-estradiol, prazosin, and SFF550 (26). Thus, it appears that hOCT1 and hOCT2 exhibit distinct substrate recognition properties depending on the substrate.

Aflatoxin B1 is mainly responsible for toxicity in both acute and chronic aflatoxicosis (27). Epidemiological studies have demonstrated that aflatoxin B1 ingestion is an important risk factor for hepatocellular cancer in humans (28). Oral administration of aflatoxin B1 at 5 mg/kg for 9 weeks in rats resulted in 100% hepatocellular carcinomas (29). In addition, several outbreaks of aflatoxicosis occurring in tropical countries revealed

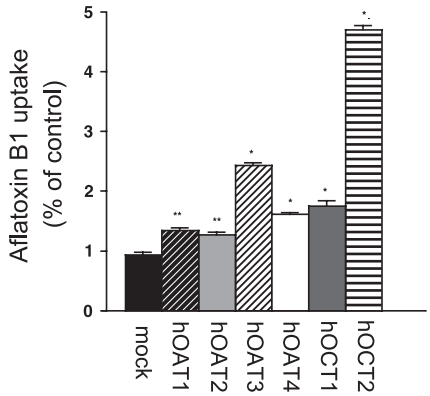


Fig. 3. Aflatoxin B1 uptake by hOATs and hOCTs. S2 hOAT1, S2 hOAT2, S2 hOAT3, S2 hOAT4, S2 hOCT1, S2 hOCT2, and mock were incubated in solution containing 100 nM [^{3}H]aflatoxin B1 at 37°C for 5 min. Each value represents the mean ± S.E.M. of six monolayers from two separate experiments. **P*<0.001 and ***P*<0.01 *vs* mock.

the induction of acute liver injury, which was confirmed by morphological examination (30). hOAT2 and hOCT1 are localized at the basolateral side of liver cells (31, 32), and the present results demonstrate that hOAT2 and hOCT1 mediate the transport of aflatoxin B1. These evidences suggest that hOAT2 and hOCT1 may contribute to the entrance for aflatoxin B1 into the liver, leading to the induction of hepatocellular carcinoma and acute hepatoxicity.

Aflatoxins have also been found in tissues of children suffering from Reye's syndrome, which is characterized by encephalopathy (33). In this regard, we found that hOAT3 mRNA is expressed in the brain (34), and the localization of hOAT1 in the blood-brain barrier was recently confirmed immunohistochemically (35). In the current study, we revealed that hOAT1 and hOAT3 mediates the transport of aflatoxin B1. These evidences suggest that hOAT1 mediates the uptake of aflatoxin B1 into the brain via the blood-brain barrier and hOAT3 is involved in the toxicological action of aflatoxin B1 within the brain.

By comparing the effects of mycotoxins on the organic anion uptake mediated by OAT1 and OAT3 between humans and rats, it was revealed that there were no interspecies differences except for the interaction of OAT3 with rubratoxin B. In addition, we have already found that there is no interspecies difference in the transport property of ochratoxin A by OAT1 between humans and rats, that is, the K_m values were 0.57 and 0.42 μM, respectively (10, 12). Further studies are necessary to clarify the effects of mycotoxins in the body using animal models like rats. In this regard, the current results may provide some information for extrapolating the results of experiments using rats to humans, although

the extrapolation to humans seems inaccurate because toxic effects of mycotoxins are mostly known in experimental models.

Although the toxic potential of citrinin and fumonisin B1 in humans has not yet been reported, citrinin has been shown to cause renal dysfunction such as glucosuria and proteinuria in rats (36), and it was recently reported that chronic exposure to fumonisin B1 induces renal tubular tumor in rats (37). Since hOAT1/rOat1 and hOAT3 /rOat3 interact with citrinin and fumonisin B1, these transporters may contribute to the basolateral uptake of these mycotoxins into the proximal tubular cells, as a first step in the development of nephrotoxicity. However, our data indicate that in different species, different intracellular events such as metabolism may also play a pivotal role in mycotoxin-induced nephrotoxicity as compared to the transport of mycotoxins into the cell. Since there is no report on toxicological roles of citrinin and fumonisin B1 in humans, we should also consider the interspecies differences in cellular events that lead to the induction of mycotoxin-induced nephrotoxicity.

In addition to the hOAT and hOCT families, it should be elucidated whether other human transporters and human homologues of rodent transporters mediate the transport of mycotoxins. In this regard, the following results have already been presented, that is, aflatoxin B1 transport by multidrug resistance-associated proteins 1 (38), ochratoxin A transport by organic anion transporting polypeptide (9), and the interaction of multidrug resistance–associated proteins 2 with ochratoxin A (11). Further studies are necessary to clarify their role as a transport pathway.

In conclusion, hOATs, rOats, and hOCTs interact with various mycotoxins. It is suggested that hOATs, rOats, and hOCTs are the potential entrance pathway for mycotoxins mainly in kidneys and liver, leading to the induction of adverse effects in humans and rats.

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