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Molecular mechanisms of organic cation transport in OCT2-expressing *Xenopus* oocytes

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Abstract

The molecular mechanisms of organic cation transport by rat OCT2 was examined in the *Xenopus* oocyte expression system. When extracellular Na^+ ions were replaced with K^+ ions, uptake of tetraethylammonium (TEA) by OCT2-expressing oocytes was decreased, suggesting that TEA uptake by OCT2 is dependent on membrane potential. Kinetic analysis revealed that the decreased TEA uptake by ion substitution was caused at least in part by decreased substrate affinity. Acidification of extracellular buffer resulted in decreased uptake of TEA, whereas TEA efflux from OCT1- and OCT2-expressing oocytes was not stimulated by inward proton gradient, in consistent with basolateral organic cation transport in the kidney. Inhibition of TEA uptake by various organic cations revealed that apparent substrate spectrum of OCT2 was similar with that of OCT1. However, the affinity of procainamide to OCT1 was higher than that to OCT2. Uptake of 1-methyl-4-phenylpyridinium was stimulated by OCT2 as well as OCT1, but uptake of levofloxacin, a zwitterion, was not stimulated by both OCTs. These results suggest that OCT2 is a multispecific organic cation transporter with the characteristics comparable to those of the basolateral organic cation transporter in the kidney.

Keywords: Organic cation transporter; OCT1; OCT2; Renal tubular secretion; (*Xenopus* oocyte)

1. Introduction

Organic cation transport in the renal tubules is an important physiological function for the maintenance of body fluid homeostasis and detoxification of harmful organic cations [1,2]. In general, transport of organic cations in brush-border membranes is mediated by the H^+/organic cation antiporter [3–7], whereas transport of organic cations in basolateral membranes is stimulated by the inside-negative membrane potential [4,8,9]. Studies using kidney epithelial cells, cultured on porous membrane filters demonstrated that transcellular transport of tetraethylammonium was regulated by apical pH [10]. By the expression cloning method, the organic cation transporter OCT1 which is expressed in rat liver and kidney was isolated [11]. In 1996, we isolated another organic cation transporter, OCT2, which is localized exclusively in the renal medulla and cortex [12]. OCT2 was deduced to be a glycoprotein comprised of 593 amino acid residues with 12 putative transmembrane domains. Although OCT2 stimulated transport of tetraethylammonium, a prototype organic cation, its detailed functional characteristics were still unclear. In this study, we utilized the *Xeno-*

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pus oocyte expression system for analyses of the functional characteristics of OCT2.

2. Materials and methods

2.1. Materials

[1-^{14}C]Tetraethylammonium bromide (185 MBq/mmol) and *N*-[*methyl*-^{3}H]1-methyl-4-phenylpyridinium acetate (3.11 TBq/mmol) were obtained from Du Pont–New England Nuclear Research Products (Boston, MA). [^{14}C]Levofloxacin (1.07 GBq/mmol) and unlabeled levofloxacin were kindly supplied by Daiichi Seiyaku Co. (Tokyo, Japan). Quinidine sulfate, cimetidine, tetraethylammonium bromide, choline chloride, *p*-aminohippuric acid, Hepes (2-(4-(2-hydroxyethyl)-1-piperazinyl)ethanesulfonic acid) and MES (2-(*N*-morpholino)ethanesulfonic acid) were purchased from Nacalai Tesque (Kyoto, Japan), and valinomycin, (−)-nicotine hydrogen tartrate, procainamide hydrochloride and N^1-methylnicotinamide iodide were purchased from Sigma Chemical Co. (St. Louis, MO, USA). 1-Methyl-4-phenylpyridinium iodide was from Research Biochemicals Incorporated (Natick, MA, USA). 1,1′-Diethyl-2,2′-cyanine iodide (decynium22) was from Aldrich Chemical Co. (Tokyo, Japan). Cephalexin was a gift from Shionogi (Osaka, Japan). All other chemicals were of the highest purity available.

2.2. Functional expression of organic cation transporter in Xenopus laevis oocytes

Aliquots of 25 ng of capped RNAs transcribed in vitro from *Not*I-linearized OCT1 and OCT2 cDNA with T3 and SP6 RNA polymerase, respectively, were injected into *Xenopus* oocytes [12]. Injected oocytes were maintained in modified Barth's medium at 18°C for 1–5 days. Functional expression of OCT2 was analyzed by measuring uptake of [^{14}C]tetraethylammonium bromide in groups of oocytes injected with 50 nl of water or RNA as described previously [13]. Oocytes were preincubated for 15 min at 25°C in uptake buffer (in mM: 100 NaCl, 2 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 Hepes (pH 7.4)), followed by a 1- or 2-h incubation with [^{14}C]tetraethylammonium bromide in the same uptake buffer (25°C) except where otherwise noted. In most experiments, uptake buffer with the following composition (low K^+ buffer) was used (in mM: 101 NaCl, 1 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 Hepes (pH 7.4)). In the pH experiments, Hepes was adjusted to pH 6.4 and 8.0, and MES (pH 5.4 and 6.0) was used instead of Hepes. High K^+ buffer (in mM: 2 NaCl, 100 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 Hepes (pH 7.4)) was used in some experiments. In the inhibition studies, various organic molecules were dissolved in the low K^+ buffer, and then uptake of [^{14}C]tetraethylammonium was measured. At the end of the uptake periods, oocytes were washed three times in 1.5 ml of ice-cold uptake buffer (pH 7.4), solubilized in 10% SDS solution, and then the radioactivity was determined in 5 ml of ACSII (Amersham) by liquid scintillation counting.

2.3. Statistical analyses

Statistical analyses were performed by one-way analysis of variance followed by Fisher's *t*-test or Dunnett's test. *P* values of less than 0.05 were considered to be significant.

3. Results

3.1. Effects of ion composition on tetraethylammonium uptake by Xenopus oocytes expressing rat OCT2

In physiological buffer, *Xenopus* oocytes form a transmembrane electrical potential, which can be decreased by replacing Na^+ ions with K^+ ions. To characterize the molecular mechanisms responsible for the transport of organic cations by OCT2, we examined the effects of ion composition of uptake buffer on tetraethylammonium uptake by OCT2-expressing oocytes. As shown in Fig. 1, when low K^+ buffer (containing 101 mM Na^+ and 1 mM K^+) was replaced with high K^+ buffer (containing 2 mM Na^+ and 100 mM K^+), tetraethylammonium uptake by OCT2-expressing oocytes was moderately decreased (69% of that in low K^+ buffer). When 7 μM valinomycin, a K^+ ionophore, was added to the high K^+ buffer, tetraethylammonium uptake by the OCT2-expressing oocytes decreased further (56% of that in

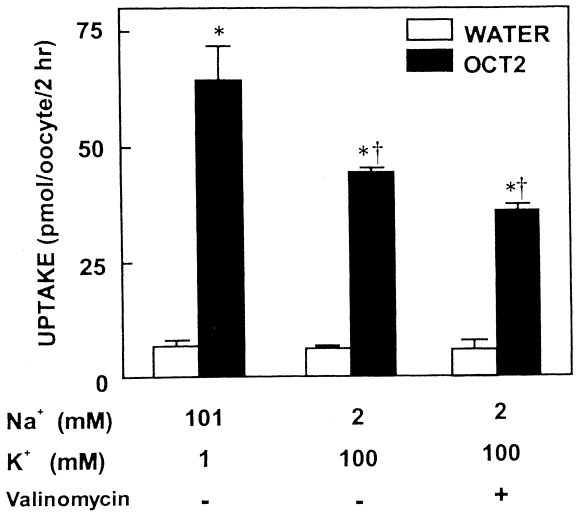

Fig. 1. Effects of buffer ion compositions on tetraethylammonium uptake by oocytes injected with water or OCT2 RNA. Uptake by oocytes was assayed for 2 h at 25°C in low K^+ (101 mM Na^+ and 1 mM K^+) and high K^+ (2 mM Na^+ and 100 mM K^+) buffers containing 250 μM [^{14}C]tetraethylammonium in the absence or presence of 7 μM valinomycin 1 day after injection of 50 nl of water (open column) or 25 ng of OCT2 RNA (closed column). Each column represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment. $^*P < 0.05$, significant differences from each water-injected control. $^\dagger P < 0.05$, significant differences from tetraethylammonium uptake by OCT2-expressing oocytes in low K^+ buffer.

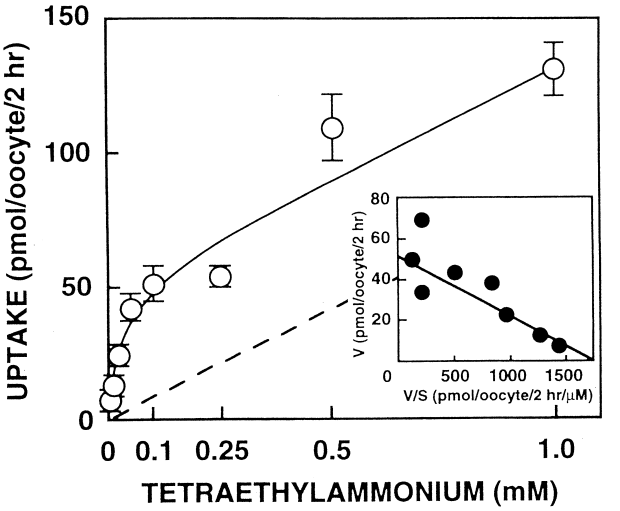

Fig. 2. Concentration dependence of tetraethylammonium uptake by *Xenopus* oocytes injected with OCT2 RNA in low K^+ buffer. Uptake by oocytes was assayed for 2 h at 25°C in low K^+ buffer containing various concentrations of [^{14}C]tetraethylammonium 2 days after injection of 25 ng of OCT2 RNA. Inset shows Eadie–Hofstee plots for the experiment. Broken line indicates the simple diffusion component calculated. Each point represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment.

low K^+ buffer). On the other hand, tetraethylammonium uptake by water-injected oocytes was not affected by the change in buffer composition.

3.2. *Concentration dependence of tetraethylammonium uptake by OCT2-expressing oocytes in low and high K^+ buffers*

To analyze the characteristics of organic cation transport by OCT2, the concentration dependence of tetraethylammonium uptake was measured in low K^+ (Fig. 2) and high K^+ (Fig. 3) buffers. In both experiments, tetraethylammonium uptake by OCT2-expressing oocytes was saturated at high concentrations. Evaluation of kinetic constants by nonlinear least-squares regression analysis [14] according to the Michaelis–Menten equation revealed that apparent Michaelis constants (K_m) were 33.8 μM for low K^+ buffer and 140 μM for high K^+ buffer, respectively. In addition, maximal transport activities

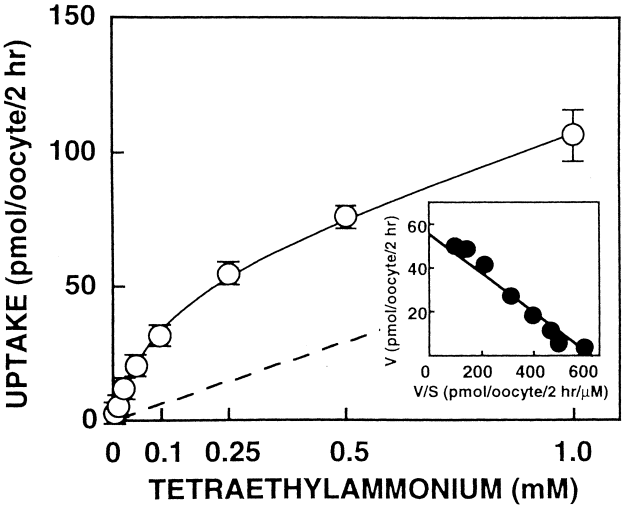

Fig. 3. Concentration dependence of tetraethylammonium uptake by *Xenopus* oocytes injected with OCT2 RNA in high K^+ buffer. Uptake by oocytes was assayed for 2 h at 25°C in high K^+ buffer containing various concentrations of [^{14}C]tetraethylammonium 2 days after injection of 25 ng of OCT2 RNA. Inset shows Eadie–Hofstee plots for the experiment. Broken line indicates the simple diffusion component calculated. Each point represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment.

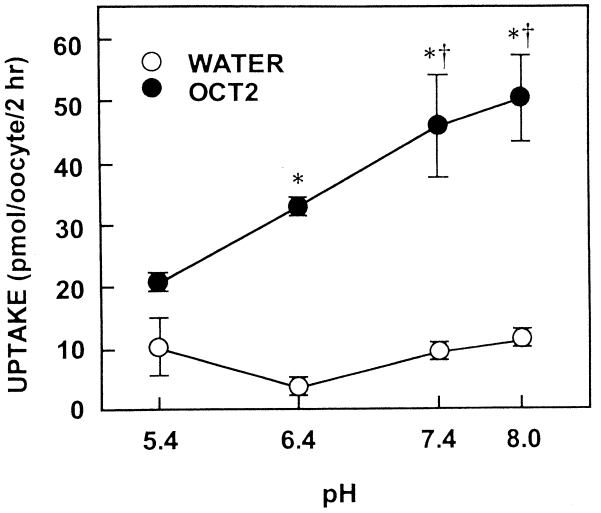

Fig. 4. Effects of buffer pH on tetraethylammonium uptake by oocytes injected with water or OCT2 RNA. Uptake by oocytes was assayed for 2 h at 25°C in low K^+ buffer at various pHs containing 250 μM [^{14}C]tetraethylammonium 1 day after injection of 50 nl of water (○) or 25 ng of OCT2 RNA (●). Each point represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment. $^*P < 0.05$, significant differences from each water-injected control. $^\dagger P < 0.05$, significant differences from tetraethylammonium uptake by OCT2-expressing oocytes at pH 5.4.

(V_{max}) were obtained as 55.5 and 66.6 pmol/oocyte per 2 h for low K^+ and high K^+ buffers, respectively. The coefficients of simple diffusion (K_d) were 82.2 and 48.1 pmol/oocyte/2 h per mM for low K^+ and high K^+ buffers, respectively.

3.3. *Effects of extracellular pH on tetraethylammonium uptake by Xenopus oocytes expressing rat OCT2*

Next, we examined the effects of pH on tetraethylammonium uptake by *Xenopus* oocytes expressing rat OCT2 (Fig. 4). Tetraethylammonium uptake by OCT2-expressing oocytes decreased according to the acidification of the uptake buffers, although tetraethylammonium uptake by water-injected controls was not affected by extracellular pH. To further clarify the pH dependence of OCT1 and OCT2, the effects of pH on efflux of [^{14}C]tetraethylammonium from OCT1- and OCT2-expressing oocytes were examined. As shown in Table 1, acidification of extracellular media from 7.4 to 6.0 did not stimulate the efflux of [^{14}C]tetraethylammonium.

3.4. *Effects of various organic ions on tetraethylammonium uptake by rat OCT1 and OCT2*

To clarify the substrate spectrum of OCT2, we examined the effects of various organic ions on tetraethylammonium uptake by OCT2-expressing oocytes. In the presence of 5 mM quinidine, unlabeled tetraethylammonium, nicotine, or levofloxacin, [^{14}C]tetraethylammonium uptake by OCT2 was decreased compared to that in control oocytes (Fig. 5). In addition, cephalexin, which is known to be transported by the H^+/organic cation antiporter in the brush-border membranes but not by basolateral organic cation transporter [15], did not inhibit tetraethylammonium uptake by OCT2.

To compare the substrate spectrum of OCT1 and OCT2, inhibitory effects of various organic ions on

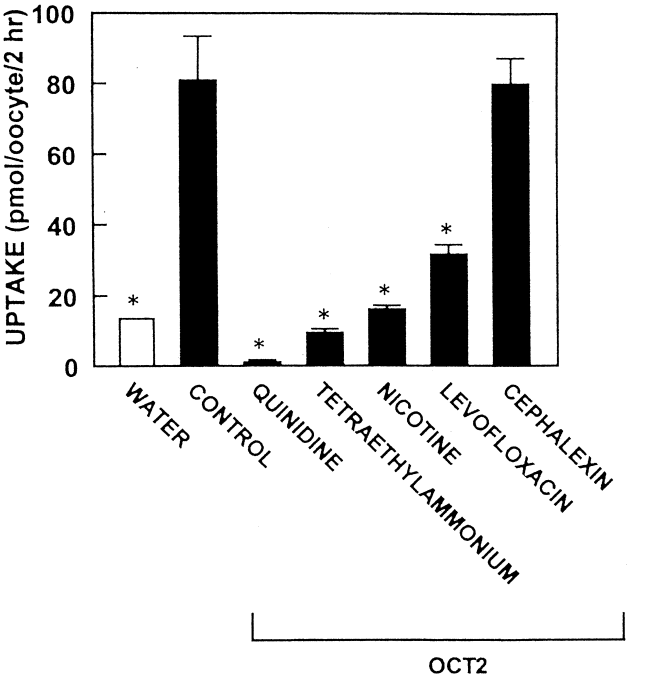

Fig. 5. Effects of various organic ions on tetraethylammonium uptake by *Xenopus* oocytes injected with water or OCT2 RNA. Uptake by oocytes was assayed for 2 h at 25°C in low K^+ buffers containing 250 μM [^{14}C]tetraethylammonium with and without 5 mM quinidine, unlabeled tetraethylammonium, nicotine, levofloxacin, and cephalexin 2 days after injection of water and 50 nl of water (open column) or 25 ng of OCT2 RNA (closed column). Each point represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment. $^*P < 0.05$, significant differences from control.

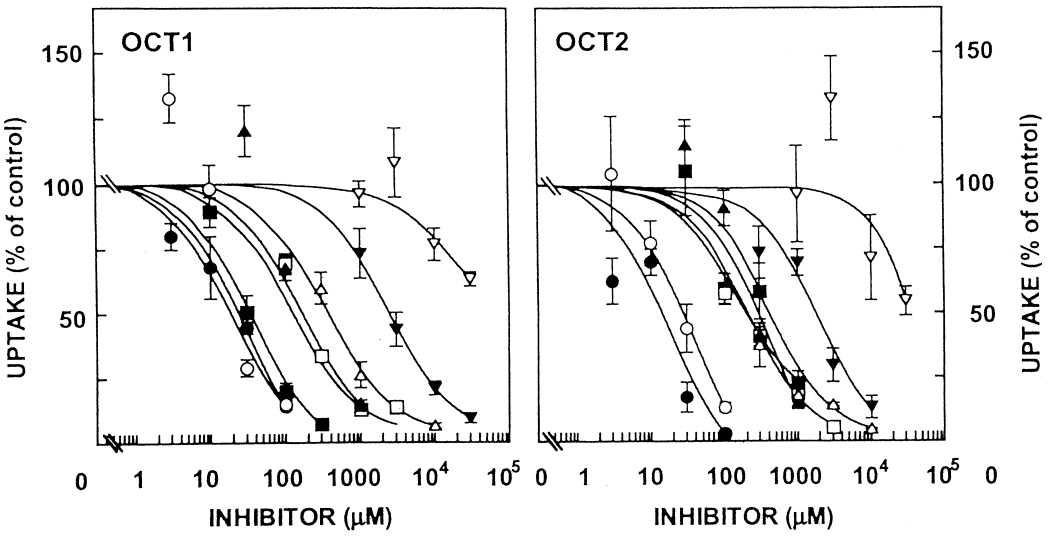

Fig. 6. Effects of various organic cations and *p*-aminohippurate on tetraethylammonium uptake by *Xenopus* oocytes injected with OCT1 or OCT2 RNA. Uptake by oocytes was assayed for 1 h at 25°C in low K^+ buffer containing 100 μM [^{14}C]tetraethylammonium in the presence of decynium22 (●), 1-methyl-4-phenylpyridinium (○), procainamide (■), tetraethylammonium (□), cimetidine (▲), choline (△), N^1-methylnicotinamide (▼) and *p*-aminohippurate (▽), 3 days after injection of 25 ng of OCT1 (left) or OCT2 (right) RNAs. Uptake values of [^{14}C]tetraethylammonium for OCT1 and OCT2 in the absence of various organic ions were 14.9 ± 0.8 and 16.5 ± 0.8 pmol/oocyte per h, respectively. Each point represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment.

[^{14}C]tetraethylammonium transport by both OCT1 and OCT2 were examined, and then concentrations for half-maximal inhibition (IC_{50}) were evaluated (Fig. 6). Inhibitory potencies of organic cations except procainamide on tetraethylammonium uptake by OCT2-expressing oocytes were comparable to those obtained for OCT1-expressing oocytes (Table 2). IC_{50} of procainamide for tetraethylammonium transport by OCT2 was about 6-fold that by OCT1.

3.5. Uptake of ionic drugs by Xenopus oocytes expressing OCT1 and OCT2

As shown in Fig. 7, uptake of [^{14}C]tetraethylammonium and [^{3}H]1-methyl-4-pheylpyridinium, organic cations, were markedly elevated compared to water-injected controls. However, uptake of [^{14}C]levofloxacin, a zwitterion, was not stimulated by either OCT1 or OCT2.

Table 1
Effect of pH on efflux of [^{14}C]tetraethylammonium from OCT1- and OCT2-expressing oocytes

	Remaining radioactivity (%)			
	OCT1		OCT2	
	pH 6.0	pH 7.4	pH 6.0	pH 7.4
30 min	104.3 ± 8.9	90.9 ± 8.9	96.8 ± 6.2	106.3 ± 5.5
180 min	95.6 ± 4.9	93.7 ± 5.7	100.0 ± 5.2	89.5 ± 5.8

Two days after injection of 25 ng of OCT RNAs, oocytes were incubated with 100 μM [^{14}C]tetraethylammonium for 16 h at 18°C in modified Barth's medium, and then incubated in low K^+ buffer without [^{14}C]tetraethylammonium (pH 6.0 or 7.4) for 30 or 180 min at 25°C. Uptake values of control oocytes (without efflux) were 70.4 ± 8.4 and 80.3 ± 15.6 pmol/oocyte, for OCT1 and OCT2, respectively. Data were expressed as the percentages of remaining radioactivity in the oocytes. Data represent the mean ± S.E. of four experiments. Three oocytes were used for each uptake experiment.

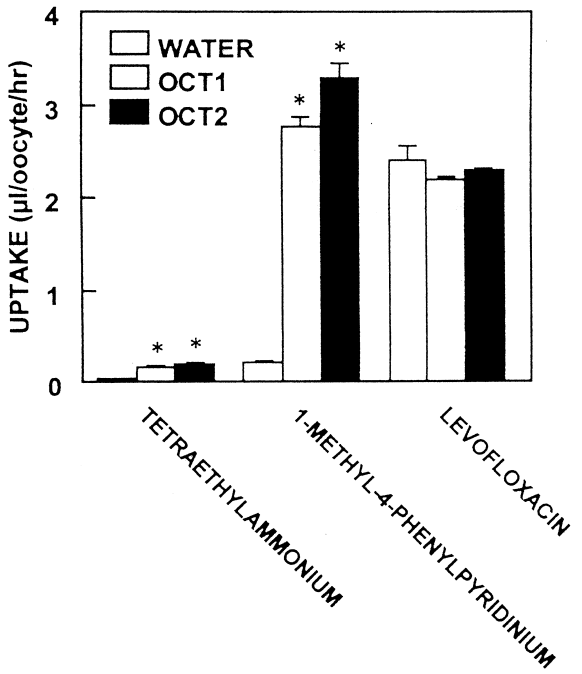

Fig. 7. Uptake of tetraethylammonium, 1-methyl-4-phenylpyridinium, and levofloxacin by *Xenopus* oocytes injected with water, OCT1 or OCT2 RNA. Uptake by oocytes was assayed for 1 h at 25°C in low K^+ buffer containing 250 μM [^{14}C]tetraethylammonium, 10 μM [^{3}H]1-methyl-4-phenylpyridinium, or 5 μM [^{14}C]levofloxacin 5 days after injection of 50 nl of water (open column), 25 ng of OCT1 (dotted column) or OCT2 (closed column) RNAs. Each column represents the mean ± S.E. of four experiments. Four oocytes were used for each uptake experiment. $*P < 0.05$, significant differences from each water-injected control.

4. Discussion

Organic cation transporters in the brush-border and basolateral membranes are clearly distinguished by the driving forces, i.e., organic cation transport in the brush-border membranes is stimulated by an oppositeward proton gradient, whereas basolateral organic cation transport is stimulated by inside-negative membrane potential. These mechanisms contribute to the efficient secretion of cationic drugs and xenobiotics in the kidney. In the present study, we examined the molecular characteristics of the organic cation transporter OCT2 by tracer uptake study using the *Xenopus* oocyte expression system. The driving force of OCT2 was comparable to that in the basolateral membranes of renal tubules. In addition, affinities of organic cations, except procainamide, for OCT1 and OCT2 were similar.

Uptake of tetraethylammonium by OCT2-expressing oocytes was decreased by replacing Na^+ ions with K^+ ions, suggesting that tetraethylammonium transport by OCT2 is dependent on membrane potential (Fig. 1). A similar phenomenon was also demonstrated for tetraethylammonium uptake by OCT1-expressing oocytes [11] and electrogenicity of organic cation transport by OCT1 was confirmed in a study using voltage-clamped *Xenopus* oocytes [16]. In the present study, the apparent K_m value for tetraethylammonium uptake by OCT2-expressing oocytes was increased by elevating extracellular K^+ concentration (Figs. 2 and 3), suggesting that the decrease of tetraethylammonium uptake by OCT2-expressing oocytes is at least in part due to a decrease in the substrate affinity. Kim and Dantzler [17] reported that elevation of K^+ concentration in incubation buffer decreased affinity of basolateral organic cation transporter for tetraethylammonium, but not altered maximal transport activity in isolated snake renal proximal tubules. Our present results seems to be consistent with their report.

Table 2
IC_{50} values for organic cations to compete with the [^{14}C]tetraethylammonium uptake by OCT1- and OCT2-expressing oocytes

Compounds	IC_{50} values for tetraethylammonium uptake[a]	
	OCT1 (μM)	OCT2 (μM)
Decynium22	21.9	13.8
1-Methyl-4-phenylpyridinium	64.1	44.2
Procainamide	44.4	257
Tetraethylammonium	167	142
Choline	398	159
Cimetidine	329	373
N^1-Methylnicotinamide	2420	1560

[a]IC_{50} values were calculated by nonlinear regression analyses using the data in Fig. 6.

As shown in Fig. 4, acidification of extracellular buffer inhibited tetraethylammonium uptake by OCT2-expressing oocytes, suggesting that the transport of tetraethylammonium by OCT2 is pH-dependent. In our previous study, accumulation of tetraethylammonium from basolateral side of LLC-PK_1 cells was markedly decreased by acidification of incubation buffer [18]. Kim and Dantzler [19] also reported that, in the isolated snake proximal tubules, tetraethylammonium transport across basolateral membranes was decreased with lowering extracellular pH. Therefore, apparent pH-dependence of tetraethylammonium uptake by OCT2-expressing oocytes could be comparable with basolateral uptake of tetraethylammonium in the renal tubules. In addition, acidification of extracellular medium did not stimulate the efflux of tetraethylammonium from OCT1- and OCT2-expressing oocytes (Table 1), suggesting that neither OCT1 nor OCT2 was driven by inward proton gradient.

Gründemann et al. [20] reported cDNA cloning of the organic cation transporter OCT2p from LLC-PK_1 cells, which is homologous to rat OCT2. They demonstrated that transport of tetraethylammonium by OCT2p was 'pH-dependent', and OCT2p was responsible for apical-type organic cation transporter in LLC-PK_1 cells. However, similar pH-dependence was observed in basolateral organic cation transport as shown by us [18] and Kim and Dantzler [19]. Membrane localization of rat OCT2 and OCT2p should be clarified further by immunological study.

It is well established that organic cation transport systems accept a wide variety of cationic molecules. In this study, levofloxacin, a zwitterionic molecule, moderately inhibited tetraethylammonium uptake by OCT2-expressing oocytes. Previously, we reported that levofloxacin strongly inhibited apical organic cation transport, and moderately interacted with basolateral organic cation transport in renal epithelial cells [21,22]. Inhibitory effect of levofloxacin on tetraethylammonium transport by OCT2 could be comparable to that described in our previous reports. As levofloxacin uptake by OCT2-expressing oocytes was not specifically stimulated, we concluded that levofloxacin was recognized by OCT2, but was not translocated.

In conclusion, OCT2 recognizes a wide variety of organic cations, showing characteristics comparable to the basolateral organic cation transport system in the kidney. Thus, OCT2 may play important physiological roles in the elimination of cationic drugs and xenobiotics in the kidney.

Acknowledgements

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