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Transport mechanism and affinity of [99mTc]Tc-mercaptoacetyltriglycine ([99mTc]MAG3) on the apical membrane of renal proximal tubule cells

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ABSTRACT

Technetium-99m-labeled mercaptoacetyltriglycine ([99mTc]MAG3) is widely used for evaluation of transplanted kidneys, diagnosis of tubular necrosis, and scintigraphic studies of tubular function. [99mTc]MAG3 is a substrate for organic anion transporter (OAT)1 and OAT3 on the basolateral membrane side for renal secretion. We investigated the transport mechanism and affinity of [99mTc]MAG3 on the apical membrane of renal proximal tubule cells for renal secretion. Adenosine triphosphate-binding cassette (ABC) transporters for renal secretion of [99mTc]MAG3 were examined using ABC transporter vesicles expressing multiple drug resistance 1 (MDR1), breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP)2, and MRP4. MK-571, a MRP inhibitor, was applied to measure the K_m and V_{max} of MRP2 and MRP4 in a vesicle transport assay. Single photon emission computed tomography (SPECT) was performed in normal rats and MRP2-deficient Eisai hyperbilirubinuria rats (EHBR) using [99mTc]MAG3 with and without MK-571. [99mTc]MAG3 uptake in adenosine triphosphate was significantly higher than that in adenosine monophosphate in vesicles that highly expressed MRP2 and MRP4. The affinity of [99mTc]MAG3 for MRP4 was higher than that for MRP2. Renal secretion via MRP2 and MRP4 was identified by comparing normal and EHBR rats with and without MK-571 on SPECT. [99mTc]MAG3 is transported via MRP2 and MRP4 on the apical membrane of renal proximal tubule cells. The affinity of MRP4 is higher than that of MRP2.

Significance statement: [99mTc]MAG3, widely used for evaluation of transplanted kidneys, diagnosis of tubular necrosis, and scintigraphic studies of tubular function, is transported via MRP2 and MRP4 on the apical membrane of renal proximal tubule cells. The affinity of MRP4 is higher than that of MRP2.

1. Introduction

Urinary excretion of drugs is determined by glomerular filtration, tubular secretion, and reabsorption from the urine. In renal scintigraphy, technetium-99m-labeled mercaptoacetyltriglycine ([99mTc]MAG3) is widely used for evaluation of transplanted kidneys, diagnosis of tubular necrosis, and scintigraphic studies of tubular function [1]. [99mTc]MAG3 is a substrate for organic anion transporter (OAT) 1 in cDNA-transfected cells, suggesting that OAT1 accounts for the kidney uptake of [99mTc]MAG3 on the basolateral membrane side from blood for renal secretion [2]. In renal proximal tubule cells, not only OAT1 but also OAT3 and organic cation transporter 2 are mainly expressed on the basolateral membrane; these transporters are classified as solute carrier transporters [4]. The transport activity of [99mTc]MAG3 in OAT1-expressing cells is higher than in OAT3-expressing cells [3].

On the other hand, ATP-binding cassette (ABC) transporters are mainly located on the apical membrane of renal proximal tubule cells and include multidrug resistance protein 1 (MDR1), breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP) 2,

Abbreviations: [99mTc]MAG3, technetium-99 m-labeled mercaptoacetyltriglycine; OAT, organic anion transporter; ATP, adenosine triphosphate; ABC, adenosine triphosphate-binding cassette; MDR1, multidrug resistance protein 1; BCRP, breast cancer resistance protein; MRP2, multidrug resistance-associated protein 2; MRP4, multidrug resistance-associated protein 4; SPECT, single photon emission computed tomography; PET, positron emission tomography; CT, computed tomography; AMP, adenosine monophosphate; EHBR, Eisai hyperbilirubinuria rat.

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MRP4 [4,5]. Among these ABC transporters, MDR1, BCRP, MRP2, and MRP4 are likely to be involved in efflux of organic anion drugs such as [^{99m}Tc]MAG3 (Fig. 1). However, the transport mechanism and affinity of [^{99m}Tc]MAG3 on the apical membrane of renal proximal tubule cells are unknown. In this study, we investigated the transport mechanism and affinity of [^{99m}Tc]MAG3 on the apical membrane in renal secretion.

2. Materials and methods

2.1. Materials

[^{99m}Tc]MAG3 was purchased from Nihon Medi-Physics Co., Ltd. (Chiba, Japan). MK-571 sodium salt was purchased from Cayman Chemical (Ann Arbor, MI, USA).

2.2. Vesicles

To investigate ABC transporters, we used vesicles (GenoMembrane Inc., Kanagawa, Japan) with high expression of human MDR1, MRP2, MRP4, or BCRP. Experimental kits were also purchased from GenoMembrane Inc. and were used for experiments for each ABC transporter.

2.3. Transport assays with vesicles overexpressing ABC transporters

Transport via ABC transporters was measured using vesicles overexpressing MDR1, MRP2, MRP4, or BCRP. These vesicles were preincubated for 10 min in reaction buffer (10 mM HEPES-Tris, 100 mM KNO_3, 10 mM $Mg(NO_3)_2$, 50 mM sucrose). [^{99m}Tc]MAG3 (37 kBq) was incubated with each vesicle solution for 5 min with ATP or adenosine monophosphate (AMP), and radioactivity was measured using a gamma counter (AccuFLEXγ7000, Aloka, Tokyo, Japan). Uptake of [^{99m}Tc]MAG3 in ATP solution was compared with that in AMP. For analyzing affinity of MRP2 and MRP4, MK-571 (1.0, 1.3, 1.5, 2.0, 2.5, 5.0, 7.5, 10, 25, 50, 100 μM), a MRP inhibitor, was added in the transport assay with vesicles to measure the K_m and V_{max} using Michaelis–Menten model. At the end of the incubation, each well was rapidly washed twice with 1 ml ice-cold *buffer* (100 μM HEPES-Tris, 1 mM KNO_3, 0.5 mM sucrose). The radioactivity of each sample was measured using the gamma counter. The vesicles were then solubilized in 0.5 ml 0.1 N NaOH, and the protein concentration was measured using a BCA Protein Assay Kit (Thermo Fisher Scientific, Kanagawa, Japan). All samples were examined in quadruplicate.

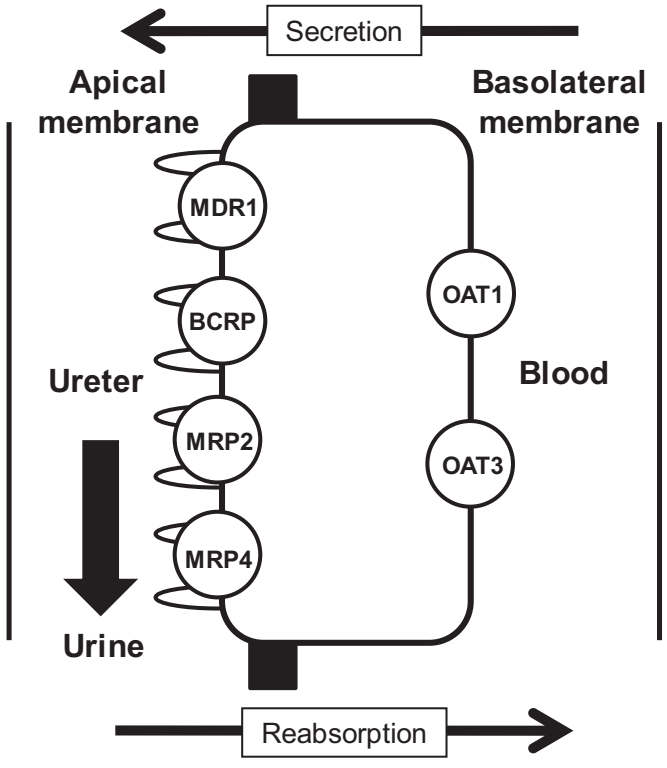

Fig. 1. Transport systems for organic anion drugs in the epithelial cells of renal proximal tubule cells. For secretion of [^{99m}Tc]MAG3, the transport system includes the organic anion transporter (OAT)1 and OAT3 on the basolateral membrane and multidrug resistance protein 1 (MDR1), breast cancer resistance protein (BCRP), multidrug resistance-associated protein (MRP)2, and MRP4 on the apical membrane.

2.4. Planar imaging and biological distribution of [^{99m}Tc]MAG3 in normal rats and EHBR rats with and without MK-571 loading

Our research adhered to the Principles of Laboratory Animal Care (NIH publication #85-23, revised in 1985). All animal studies were also conducted following approval by the Animal Care Committee of Kanazawa University and Nagasaki University (AP-122340). For planar imaging, normal rats (Sprague Dawley, male, 6 weeks old, $n = 4$) and Eisai hyperbilirubinuria (EHBR) rats (male, 6 weeks old, $n = 8$) were housed under a 12-hour light/12-hour dark cycle with free access to water and food and then to only water for one night before the day of the experiment. Planar imaging with a single pinhole collimator was immediately started with an intravenous bolus administration of [^{99m}Tc]MAG3 (about 70 MBq) using a micro-injection pump (CFX1010, ISIS, Osaka, Japan) for 15–20 s into the tail vein of normal rats ($n = 4$) under 2.0–2.5% isoflurane (Abbott Laboratories, Green Oaks, IL, USA). Imaging continued for about 30 min (20 s/frame for 5 min, 30 s/frame for 5 min, and 300 s/frame for 20 min) using a small animal single photon emission computed tomography/positron emission tomography/computed tomography (SPECT/PET/CT) imaging scanner (TriFoil Imaging, Inc., Northridge, CA, USA). The data were reconstructed using maximum likelihood-expectation maximization with six iterations including attenuation and no scatter correction. The voxel size was set to 0.53 × 0.53 × 0.37 mm. Post-reconstruction smoothing filtering was applied using a 1.0-mm Gaussian filter. Image displays were obtained using Amide's a medical image data examiner, which is an open-source medical image data analysis software tool (ver. 1.04). In these images, three to five regions of interest were placed over the kidney, bladder and background radioactivity in blood, and then the each time activity curve was obtained. The background of radioactivity in blood was subtracted from the radioactivity of kidney and bladder. We determined average time-to-peak (T_{max}) and average times to half-maximal activity ($T_{1/2}$) and area under the curve (AUC). EHBR rats ($n = 4$ of 8) were imaged to evaluate the effect of MRP2 using the same protocol of SPECT/CT imaging that was used for normal rats. After radioactive decay of ^{99m}Tc in the above mentioned EHBR rats, the same EHBR rats were used for evaluation of the effect of 1.0 mM MK-571, a MRP inhibitor. The EHBR rats were injected with a mixture of [^{99m}Tc]MAG3 and MK-571, and planar imaging was immediately acquired using the same imaging protocol that was used for normal rats.

For biological distribution studies, normal SD rats (male, 6 weeks old, $n = 4$), EHBR rats (male, 6 weeks old, $n = 8$) were housed with a 12-h light/12-h dark cycle with free access to only water. Normal rats and EHBR rats (n = 4) that had fasted all night were administered [^{99m}Tc]MAG3 via the tail vein (3.7 MBq/rat). At 5, 10, and 30 min, normal rats were euthanized under isoflurane anesthesia, and the following tissues were collected: blood, liver, kidney, bladder, and muscle. Tissues were weighed, and radioactivity was quantified using a γ-ray counter to calculate the percent injected dose (radioactive cpm in tissue sample divided by cpm of injected radioactivity per gram of tissue × 100 (%ID/g)). For the MK-571 inhibition study, the EHBR rats ($n = 4$) were injected with a mixture of [^{99m}Tc]MAG3 and MK-571, and the

distribution studies were performed using the same protocol that was used for normal and EHBR rats.

2.5. Statistical analysis

Data are presented as the means and standard deviations. *P* values were calculated using the two-tailed paired Student's *t*-test for comparison between two groups and repeated-measures analysis of variance for comparison among three groups. Statistical analyses were performed with Graphpad Prism 8 software (San Diego, CA, USA). A *P* value < .05 was considered significant.

3. Results

Fig. 2 shows uptake of [^{99m}Tc]MAG3 by vesicles overexpressing ABC transporters. [^{99m}Tc]MAG3 uptake into vesicles that highly expressed MRP2 or MRP4 in the presence of ATP was significantly higher than that in the presence of AMP ($P < .01$), but not MDR1 and BCRP. Uptake by MRP4 was higher than that by MRP2. Fig. 3 shows determination of the K_m and V_{max} using MK-571 in the vesicle transport assay. The K_m values of MK-571 for MRP2- and MRP4-mediated [^{99m}Tc]MAG3 uptake were 8.1 ± 1.2 μM ($R^2 = 0.98$) and 4.5 ± 1.0 μM ($R^2 = 0.94$), respectively. The V_{max} values for MRP2- and MRP4-mediated [^{99m}Tc]MAG3 uptake were 13.3 ± 0.6 μM ($R^2 = 0.98$) and 12.8 ± 0.8 μM ($R^2 = 0.94$), respectively.

Next, we obtained SPECT images and time activity curves with rats (normal or EHBR) injected with [^{99m}Tc]MAG3 with or without MK-571 loading (Fig. 4). The time activity curves of [^{99m}Tc]MAG3 derived from SPECT images revealed the T_{max} of 4.1 ± 1.2 min, 4.0 ± 1.5 min, and 6.5 ± 1.3 min in normal rats, EHBR rats, and EHBR rats with MK-571 loading, respectively. The $T_{1/2}$ were 8.8 ± 2.1 min, 17.4 ± 3.6 min, and 20.1 ± 3.8 min in normal rats, EHBR rats, and EHBR rats with MK-571 loading, respectively. The AUC were 2.94 ± 0.61 cps × min, 3.46 ± 0.59 cps × min, and 3.49 ± 0.83 cps × min in normal rats, EHBR rats, and EHBR rats with MK-571 loading, respectively. Regarding bladder accumulation of [^{99m}Tc]MAG3, normal rats showed the highest accumulation immediately after administration, followed by EHBR rats and then EHBR rats with MK-571 loading. In Table 1, radioactivity of kidney and bladder in all rat groups were similar with time activity curves derived from SPECT images in Fig. 4b and c. There was little difference in all rat groups in liver and muscle. EHBR rats with MK-571 inhibitor yielded higher radioactivity in blood than normal and EHBR rats.

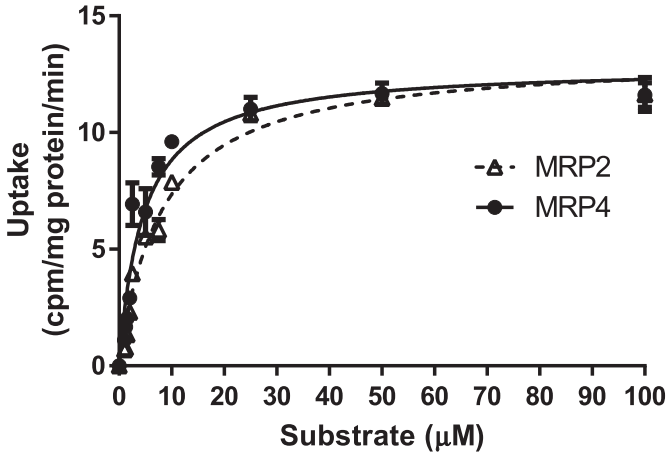

Fig. 3. Measurement of K_m and V_{max} using MK-571 (1.0, 1.3, 1.5, 2.0, 2.5, 5.0, 7.5, 10, 25, 50, 100 μM) in the transport assay with vesicles overexpressing MRP2 (Δ and dotted line) and MRP4 (● and solid line).

4. Discussion

Anion drugs are usually transported by OATs, which are solute carrier transporters, and MRPs, which are ABC transporters [4]. [^{99m}Tc]MAG3, an organic anion drug, is transported across the renal basolateral membrane via OAT1 [2] and OAT3 [3], but the transport mechanism and

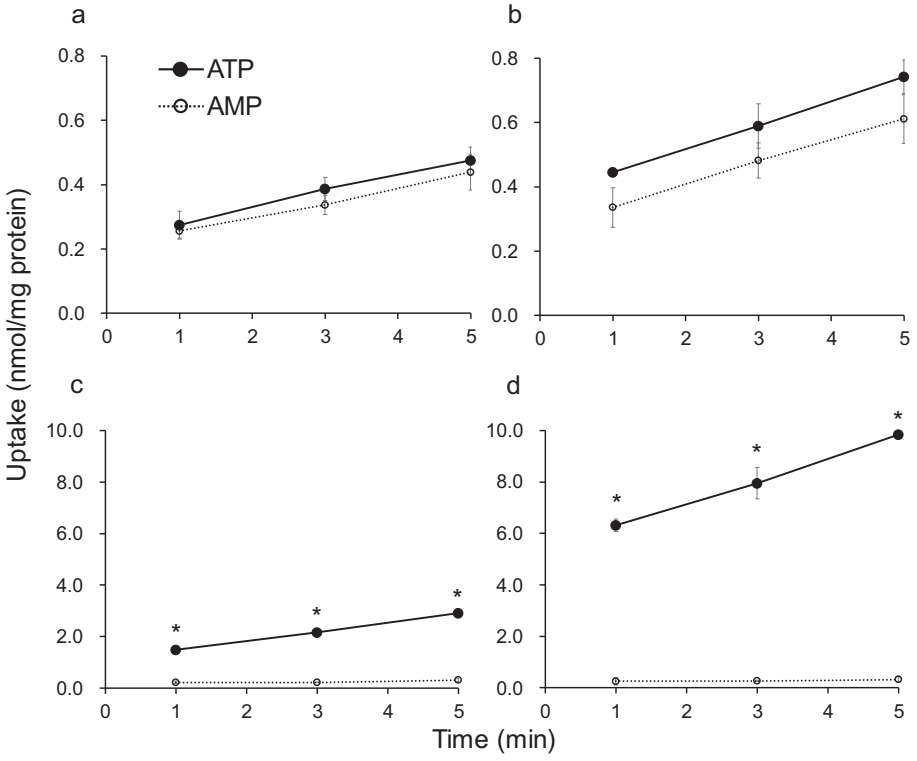

Fig. 2. Uptake of [^{99m}Tc]MAG3 by vesicles overexpressing each ABC transporter in ATP solution (● and solid line) and AMP solution (○ and dotted line) after 1, 3, and 5 min of incubation. *$P < .01$ between uptake in ATP and AMP solution ($n = 5$; paired *t*-test). a; MDR1, b; BCRP, c; MRP2 and d; MRP4.

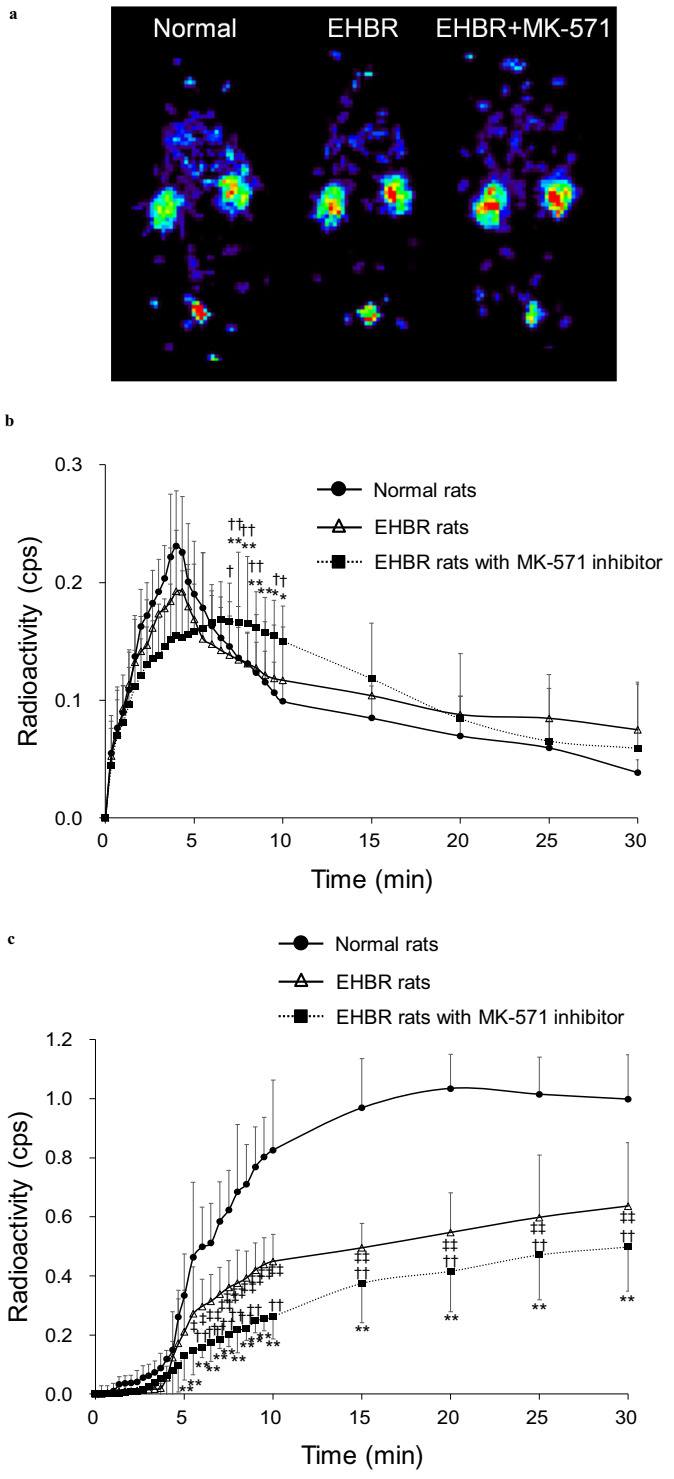

Fig. 4. SPECT images between 9 min and 10 min (a) and time activity curves in kidney (b) and bladder (c) of [^{99m}Tc]MAG3 in normal rats (●), EHBR rats (Δ), and EHBR rats with MK-571 loading (■) under 2.0% isoflurane anesthesia injected with about 70 MBq [^{99m}Tc]MAG3 for 30 min. $^{‡}P < .01$ and $^{‡‡}P < .05$ for radioactivity between normal rats and EHBR rats, $^{*}P < .01$ and $^{**}P < .05$ for radioactivity between normal rats and EHBR rats with MK-571 loading, and $^{†}P < .01$ and $^{††}P < .05$ for radioactivity between EHBR rats and EHBR rats with MK-571 loading ($n = 4$ in each group; repeated-measures analysis of variance).

the affinity for drug transporters on the apical membrane of renal proximal tubule cells were unknown. In this study, we showed that [^{99m}Tc]MAG3 was transported by MRP2 and MRP4 on the apical membrane of renal proximal tubule cells (Figs. 1 and 2). Fig. 3 showed that the affinity

Table 1
Biological distribution of [^{99m}Tc]MAG3 on control, EHBR rats and EHBR rats with MK-571 loading.

Rats	Organ (%ID/g)	5 min	10 min	30 min
Normal rats	Blood	0.52 ± 0.14	0.42 ± 0.11	0.31 ± 0.09
	Liver	0.11 ± 0.03	0.28 ± 0.08	0.35 ± 0.10
	Kidney	13.43 ± 2.91	6.45 ± 1.12	3.87 ± 0.95
	Bladder	20.89 ± 5.11	41.34 ± 5.67	56.78 ± 6.23
	Muscle	0.18 ± 0.05	0.14 ± 0.03	0.13 ± 0.04
EHBR rats	Blood	0.57 ± 0.18	0.45 ± 0.15	0.33 ± 0.12
	Liver	0.13 ± 0.05	0.31 ± 0.10	0.36 ± 0.12
	Kidney	13.11 ± 3.51	7.25 ± 2.01	$4.93^{†}$ ± 1.03
	Bladder	17.44 ± 4.45	$21.33^{††}$ ± 5.09	$33.55^{††}$ ± 4.91
	Muscle	0.15 ± 0.05	0.13 ± 0.04	0.12 ± 0.05
EHBR rats with MK-571 inhibitor	Blood	$0.99^{††,*}$ ± 0.37	$0.75^{††,*}$ ± 0.22	0.39 ± 0.13
	Liver	0.16 ± 0.08	0.34 ± 0.14	$0.45^{†}$ ± 0.14
	Kidney	9.61 ± 4.81	$12.45^{†}$ ± 3.44	3.42 ± 1.01
	Bladder	$7.67^{††,**}$ ± 3.13	$15.84^{††,*}$ ± 4.33	$27.64^{††,*}$ ± 5.78
	Muscle	0.18 ± 0.08	0.17 ± 0.05	0.16 ± 0.07

%ID/g indicates percent injected dose per gram of tissue.
Values are the mean ± standard deviation obtained from four rats.
$^{†}P < .05$ and $^{††}P < .01$ compared with normal rats and $^{*}P < .05$ and $^{**}P < .01$ compared with EHBR rats.

of [^{99m}Tc]MAG3 for MRP4 was higher than that for MRP2 because the average K_m values of [^{99m}Tc]MAG3 were 8.1 μM for MRP2 and 4.5 μM for MRP4.

Normal rats express MRP2 [6] and MRP4 [7], whereas EHBR rats lack functional MRP2. We estimated that EHBR rats with MK-571 loading would lack function of both MRP2 and MRP4. The average T_{max} values were thought to be similar in normal and EHBR rats because both OAT1 and OAT3 are expressed on the basolateral membrane in both types of rats and because MRP4 would be more involved in the transport on the apical membrane in renal proximal tubule cells than MRP2 in EHBR rats. On the other hand, MK-571-loaded EHBR rats that were administered [^{99m}Tc]MAG3 showed a slower T_{max} than the other rats, which may be because MK-571 inhibits not only MRP but also partially inhibits OAT [8]; thus, [^{99m}Tc]MAG3 uptake on the basolateral membrane was inhibited in MK-571-loaded EHBR rats.

The difference in the $T_{1/2}$ and AUC values between normal and EHBR rats showed that MRP2 was involved in [^{99m}Tc]MAG3 transport. MK-571 loading was thought to partially inhibit the function of MRP4 on the renal apical membrane, which led to the delay in the $T_{1/2}$ value in MK-571-loaded EHBR rats compared to normal and EHBR rats. Although the affinity of MRP4 was higher than that of MRP2 in vitro (Fig. 3), the effect of MRP4 would be smaller than that of MRP2 regarding $T_{1/2}$ and AUC values because the effect of MK-571 was transient after the injection. Regarding the bladder accumulation of [^{99m}Tc]MAG3, normal rats showed the highest accumulation, followed by EHBR rats and then EHBR rats with MK-571 loading. MK-571 loading for transient MRP4 inhibition in EHBR rats provided significant inhibition. Therefore, we confirmed that [^{99m}Tc]MAG3 was transported via MRP2 and MRP4 in vivo.

In biological distribution of [^{99m}Tc]MAG3 (Table 1), radioactivity of kidney and bladder in all rat groups were similar with time activity curves derived from SPECT images (Fig. 4b and c). Because radioactivity of bladder in EHBR rats and EHBR rats with MK-571 loading was lower than that in normal rats, the effect of MRP2 and MRP4 for efflux of [^{99m}Tc]MAG3 was found, but the effect of MRP4 inhibition in EHBR rats with MK-571 was smaller than the effect of MRP2 deficiency in EHBR rats like Fig. 4c because of transient MK-571 inhibition although MK-571 yielded higher radioactivity in blood than normal and EHBR rats due to OAT inhibition.

This study showed the transport mechanism of [^{99m}Tc]MAG3 in kidney, and suggested that MRP2 and MRP4 were involved in secretion of [^{99m}Tc]MAG3 from proximal tubule cells into urea and that MRP inhibitors may affect the pharmacokinetics of [^{99m}Tc]MAG3. Taylor reported that patients with renal failure show a change in the biodistribution of

[^{99m}Tc]MAG3 and an increase in accumulation in the gallbladder compared with normal subjects [9]. If the reason for these observations is low function of MRP4 on the renal apical membrane due to renal failure, the normal function of MRP2 that is expressed on the bile canalicular membrane may be involved in the increase in accumulation in the gallbladder of [^{99m}Tc]MAG3. Thus, our findings may be helpful for deciding on the use of [^{99m}Tc]MAG3 or the interpretation of the distribution of [^{99m}Tc]MAG3.

5. Conclusion

[^{99m}Tc]MAG3 is transported via OAT1 and OAT3 on the basolateral membrane from blood into tubular epithelial cells and then via MRP2 and MRP4 on the apical membrane from the cells into urine. The affinity of [^{99m}Tc]MAG3 for MRP4 is higher than that for MRP2.

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Declaration of competing interest

Hiroyuki Okudaira is an employee of Nihon Medi-Physics Co., Ltd.

Acknowledgments

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Ethical approval

All applicable institutional guidelines for the care and use of animals were followed at Kanazawa University. All procedures performed in studies involving animals were in accordance with the ethical standards of Kanazawa University (the Animal Care Committee of Kanazawa University, AP-122340).

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