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Biochemical Pharmacology 69 (2005) 993–999
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

Restored expression and activity of organic ion transporters rOAT1, rOAT3 and rOCT2 after hyperuricemia in the rat kidney

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Received 22 October 2004; accepted 13 December 2004

Abstract

We previously reported that in hyperuricemic rats, renal impairment occurred and organic ion transport activity decreased, accompanied with a specific decrease in the expression of rat organic anion transporters, rOAT1 and rOAT3, and organic cation transporter, rOCT2. In the present study, we investigated the reversibility of the organic ion transport activity and expression of organic ion transporters (slc22a) during recovery from hyperuricemia. Hyperuricemia was induced by the administration of a chow containing uric acid and oxonic acid, an inhibitor of uric acid metabolism. Four days after discontinuance of the chow, the plasma uric acid concentration returned to the normal level, and renal functions such as creatinine clearance and BUN levels were restored, although the recovery of tubulointerstitial injury was varied in sites of the kidney. Basolateral uptake of *p*-aminohippurate (PAH) and tetraethylammonium (TEA), and both protein and mRNA levels of rOAT1, rOAT3 and rOCT2 in the kidney gradually improved during 14 days of recovery from hyperuricemia. Basolateral PAH transport showed a higher correlation with the protein level of rOAT1 ($r^2 = 0.80$) than rOAT3 ($r^2 = 0.34$), whereas basolateral TEA transport showed a strong correlation with rOCT2 protein ($r^2 = 0.91$). The plasma testosterone concentration, which is a dominant factor in the regulation of rOCT2, was gradually restored during the recovery from hyperuricemia, but the correlation between the plasma testosterone level and rOCT2 protein expression in the kidney was not significant. These results suggest that the regulation of organic ion transporters, rOAT1, rOAT3 and rOCT2, by hyperuricemia is reversible, and the organic ion transport activity restores according to the expression levels of these transporters.

Keywords: Renal transport; Organic anion transporter; Organic cation transporter; slc22a; Rats; Hyperuricemia

1. Introduction

Urinary excretion of various compounds including endogenous metabolites, drugs and xenobiotics is an important physiological function of the renal proximal tubules. In renal tubules, membrane transport systems mediate the tubular secretion, and several isoforms of organic anion and cation transporters have been characterized [1,2]. Two organic anion transporters, OAT1 and OAT3, at the renal basolateral membrane mediated the renal tubular secretion of several anionic drugs including *p*-aminohippurate (PAH), nonsteroidal anti-inflammatory drugs, methotrexate and cephalosporins [3–8]. On the other hand, organic cation transporters, OCT1 and OCT2, were localized to basolateral membranes of renal tubular cells, and contributed to the transport of many cationic compounds including tetraethylammonium (TEA), cimetidine, monoamines and procainamide [8–12].

We previously reported that renal organic anion and cation transport activity across the basolateral membrane was decreased in hyperuricemic rats, accompanied with decreased expression of some organic ion transporters, rOAT1, rOAT3 and rOCT2 [13]. In contrast, the renal expression levels of rOCT1, OAT-K1 and OAT-K2, kidney-specific organic anion transporters, and organic anion transporting polypeptide 1 (oatp1) were unchanged in hyperuricemic rat kidney [13]. Renal clearances of methotrexate and cimetidine were also decreased in hyperuricemic rats, suggesting that the down-regulation of rOAT1, rOAT3 and rOCT2 partly accounts for the decreased renal disposition of these drugs [13].

Altered expression of renal organic ion transporters has been reported using several animal models with renal impairment induced by cisplatin and by subtotal nephrect-

Abbreviations: PAH, *p*-aminohippurate; TEA, tetraethylammonium

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doi:10.1016/j.bcp.2004.12.004

omy [14–17]. However, little information is available on the alterations in the expression of renal organic ion transporters during the recovery from renal impairment. On one hand, renal functions were decreased in hyperuricemic rats induced by the administration of a chow containing uric acid and oxonic acid, an inhibitor of uric acid metabolism [18]. After administration of the chow was discontinued, renal functions such as the fractional reabsorption of sodium and phosphate were improved, although the urine concentrating ability, calcium reabsorption and the capacity to excrete ammonium remained impaired [18]. Therefore, renal functions including renal organic ion transport might change at different rates during recovery from hyperuricemia in rats.

In the present study, we examined the alteration of organic ion transport activity and the expression of organic ion transporters including rOAT1, rOAT3 and rOCT2 in the kidney during recovery from hyperuricemia in rats.

2. Materials and methods

2.1. Materials

D-[1-^{3}H(*N*)]-mannitol (973 GBq/mmol) and *p*-[glycyl-1-^{14}C]-aminohippuric acid (1.9 GBq/mmol) were obtained from Perkin-Elmer™ Life Sciences. [1-^{14}C] Tetraethylammonium bromide (2.04 GBq/mmol) was obtained from American Radiolabeled Chemicals. Oxonic acid and uric acid were purchased from Aldrich and Wako Pure Chemical Industries, respectively. All other chemicals used were of the highest purity available.

2.2. Animals

The animal experiments were performed in accordance with the Guidelines for Animal Experiments of Kyoto University. The experimental protocol was approved by the Animal Research Committee, Graduate School of Medicine, Kyoto University. Male Wistar rats weighing 190–235 g were fed ground rat chow and water freely for 10–24 days. Hyperuricemia was induced with ground standard rat chow containing 2.5% uric acid and 5% oxonic acid for 10 days as described in our previous report (0-day recovery group) [13]. During recovery from hyperuricemia, the rats were fed standard rat chow for 4, 7 or 14 days (4, 7 or 14-day recovery group).

2.3. Biochemical tests

The concentration of blood urea nitrogen (BUN) and creatinine in plasma and urine were measured by the urease–indophenol method and Jaffé method using kits obtained from Wako Pure Chemical Industries, respectively. Plasma uric acid concentration was determined by high performance liquid chromatography as described in the previous report [13]. Plasma concentration of testosterone was measured with an enzyme immunoassay kit (Cayman Chemical Company).

2.4. Histological analyses

Kidneys of rats during recovery from hyperuricemia were removed and immediately fixed for 1 day at room temperature in carnoy fixative (ethanol:chloroform:acetic acid = 6:3:1) and preserved in 70% ethanol. Conventional histological sections were stained with periodic acid-Schiff reagent [8].

2.5. Uptake of PAH and TEA into renal slices

Renal slices were prepared with a Stadie–Riggs microtome and the uptake of [^{14}C]PAH (5 μM, 0.93 kBq/mL) or [^{14}C]TEA (5 μM, 1.03 kBq/mL) were measured as previously described [13]. [^{3}H]Mannitol (5 μM, 22.8 kBq/mL) was used to calculate the extracellular trapping and nonspecific uptake of [^{14}C]PAH and [^{14}C]TEA as well as to evaluate the viability of slices.

2.6. Western blot analyses

Preparation of crude membrane fractions and Western blot analyses were performed as previously reported [13].

2.7. Northern blot analyses

Total RNA was extracted from the kidney using TRIZOL™ reagent (Invitrogen Co.). Then, Northern blot analyses were performed as previously described [13].

2.8. Statistical analyses

The statistical significance of differences between mean values was calculated using the non-paired *t*-test, or by the one-way analysis of variance with the Scheffé test for post hoc analysis. *P*-values of <0.05 were considered significant.

3. Results

Several physiological and biochemical parameters were measured during the recovery period of hyperuricemia in rats (Fig. 1). The body weight gradually increased during recovery for 14 days. Plasma uric acid returned to the normal level during the initial 4 days of recovery. Improvement of BUN, plasma creatinine and creatinine clearance during the initial 4 days suggested that renal functions have been recovered quickly. In contrast, urine volume returned to normal more slowly than the above parameters.

Histological analyses of the kidney were performed and shown in Fig. 2. The tubular lumen was dilated in a diffuse

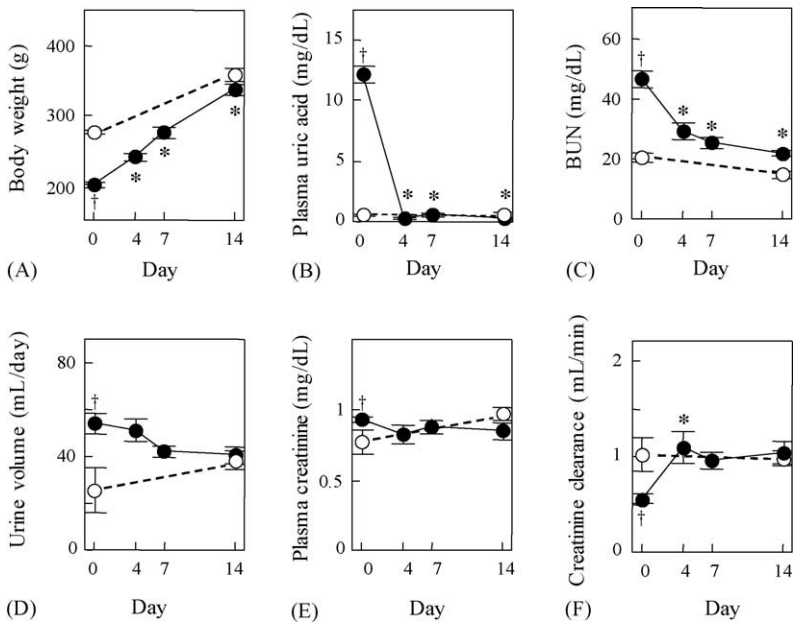

Fig. 1. Physiological and biochemical parameters during recovery from hyperuricemia. At 4, 7 and 14 days recovery from hyperuricemia, body weight (A), plasma uric acid (B), BUN (C), urine volume (D), plasma creatinine (E) and creatinine clearance (F) were measured (●). Open circles represent the values of normal rats. Each point represents the mean ± S.E. of 5–13 rats. $^{\dagger}P < 0.05$, vs. normal rats. $^{*}P < 0.05$, vs. hyperuricemic rats on day 0.

area filled with detached tubular epithelial cells and was infiltrated by mono- and poly-nuclear cells in hyperuricemic rat kidney (0-day recovery group) as previously reported [13]. Moreover, inflammatory cells also infiltrated into the interstitium and in tubules [13]. This tubulointerstitial pathology was observed in the diffuse area on day 4, and visible in the focal area on day 7, which was almost disappeared on day 14 (Fig. 2).

We then evaluated basolateral organic anion and cation transport activity by the uptake of PAH and TEA into renal slices (Fig. 3). The PAH and TEA uptake into renal slices in the 0-day recovery group were much lower than those in normal rats. In the 4-days recovery group, PAH and TEA uptake were significantly increased compared with those in 0-day recovery group. The PAH and TEA uptake in the 14-days recovery groups achieved similar uptake activity to those in control group at 30 or 60 min.

The expression of rOAT1, rOAT3 and rOCT2 protein during the recovery period of hyperuricemic rats was examined by Western blot analyses (Fig. 4). The expression of these transporters of 0-day recovery group was significantly decreased in hyperuricemic rats compared with normal rats, and the expression levels of rOAT1 and rOAT3 in 7- and 14-days recovery group significantly increased compared with those in 0-day recovery group. The expression of rOCT2 protein gradually increased until 14-days of recovery.

The mRNA expression of rOAT1 and rOCT2 during recovery from hyperuricemia was analyzed by Northern blot analyses (Fig. 5). The mRNA expression of both transporters in the 0-day recovery group was much lower than that in normal rats, and the rOAT1 mRNA expression significantly increased in the 7- and 14-days recovery group compared with 0-day recovery group. Recovery of rOCT2 mRNA expression was significant on day 14. Moreover, the expression of rOAT1 and rOCT2 protein was significantly correlated with that of mRNA, respectively (rOAT1, $r^2 = 0.66$, $P < 0.05$; rOCT2, $r^2 = 0.45$, $P < 0.05$).

We investigated the correlation between basolateral PAH and TEA transport and the protein level of rOAT1, rOAT3 and rOCT2 (Fig. 6). Initial PAH transport at 15 min across basolateral membrane showed a high correlation with the protein level of rOAT1 ($r^2 = 0.80$, $P < 0.05$), but not with that of rOAT3 ($r^2 = 0.34$, $P = 0.35$). On one hand, basolateral TEA transport showed a high correlation with the protein level of rOCT2 ($r^2 = 0.91$, $P < 0.05$).

Finally, we measured plasma concentration of testosterone, which was the dominant factor mediating sex-related difference in the expression of rOCT2 [19]. Plasma testosterone concentration was decreased in the 0-day recovery group (control, 3.23 ± 0.59 ng/mL; 0 day, 1.08 ± 0.10 ng/mL; mean ± S.E., $n = 6$) and was gradually increased during the recovery period of hyperuricemia (4 days, 1.68 ± 0.45 ng/mL; 7 days, 3.61 ± 0.24 ng/mL; 14 days, 4.51 ± 1.26 ng/mL; mean ± S.E., $n = 6$). However, plasma testosterone levels and the expression of rOCT2 protein did not show a significant linear correlation (Fig. 7, $r^2 = 0.14$, $P = 0.14$).

4. Discussion

Hyperuricemia is often the first clinical manifestation of gout and accompanies renal failure. Recently, serum uric

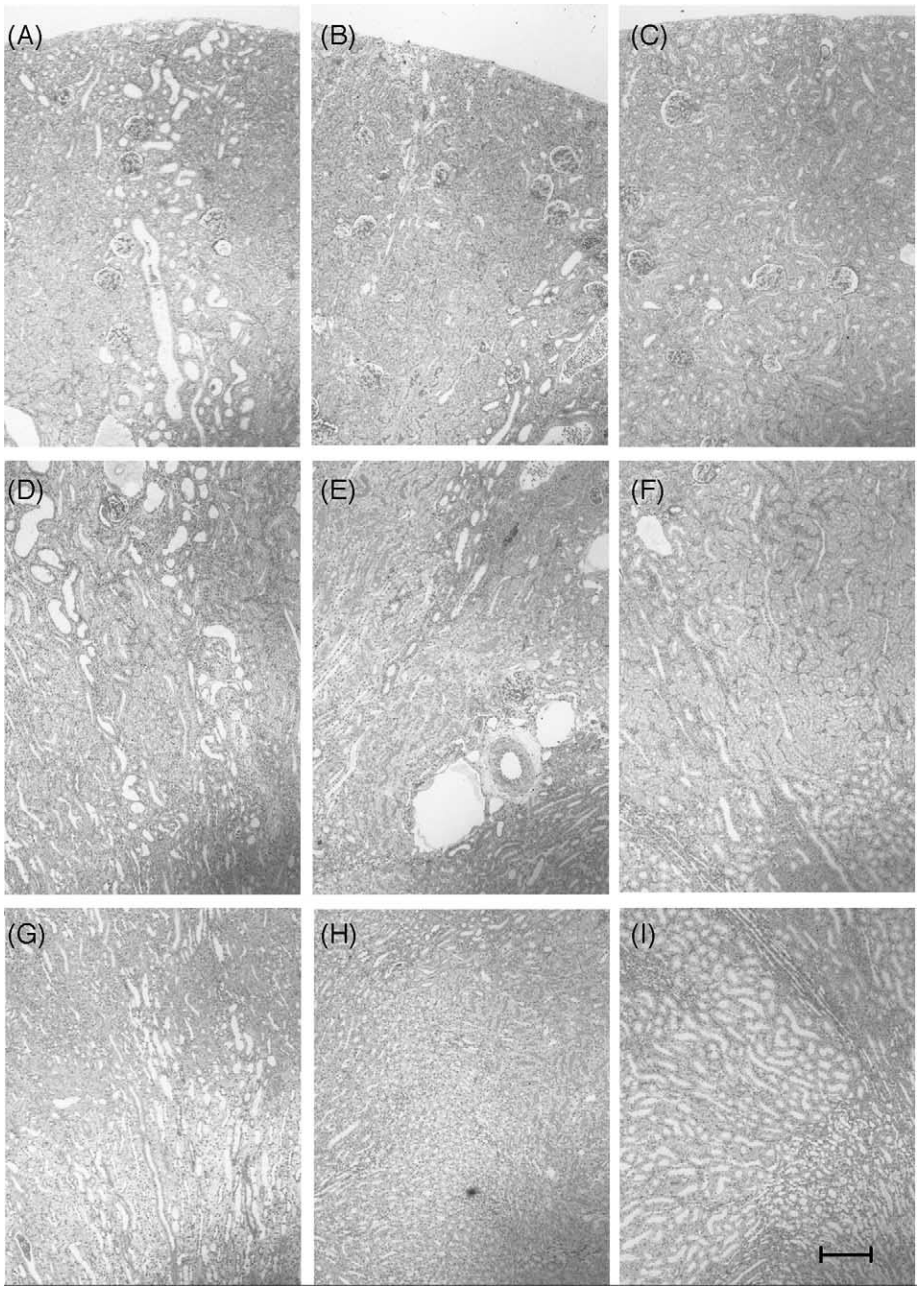

Fig. 2. Periodic acid-Schiff staining of cortex (A–C), outer medulla (D–F) and inner medulla (G–I) in the serial picture from each typical rat kidney at 4—(A, D and G), 7—(B, E and H) and 14—(C, F and I) days recovery from hyperuricemia; bar = 100 μm.

acid was found to be an independent risk factor for development of renal insufficiency in a study of 6403 subjects [20]. Mazaali et al. reported that crystal-independent mechanism, mediated in part by activation of the renin-angiotensin system and downregulation of NO synthase expression, contributed to renal injury in hyperuricemia [21]. Actually, we did not observe urate crystals in any part of kidneys in our experiments (Fig. 2). We previously reported that plasma creatinine and BUN levels increased, and that basolateral organic ion transport activity decreased, accompanied with specifically decreased expression of rOAT1, rOAT3 and rOCT2 in the kidney of hyperuricemic rats [13]. In this study, we investigated renal organic ion transport activity and the expression of rOAT1, rOAT3 and rOCT2 in kidney during recovery from hyperuricemia.

During the initial 4 days, BUN, plasma creatinine and creatinine clearance were restored significantly (Fig. 1), suggesting that renal functions recovered quickly. On the other hand, the recovery of tubulointerstitial injury was varied in sites of the kidney, probably because of the different severity of damage as shown in Fig. 2. Organic anion and cation transport activity across basolateral membranes and the expression of organic ion transporters, rOAT1, rOAT3 and rOCT2 in the kidney also gradually improved (Figs. 3 and 4). Interestingly, basolateral PAH

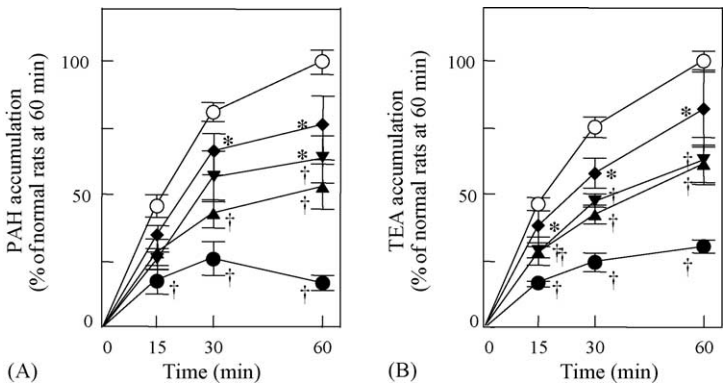

Fig. 3. Accumulation of PAH (A) and TEA (B) into renal slices during the recovery from hyperuricemia. Renal slices from normal (○) and hyperuricemic rats at 0: ●, 4: ▲, 7: ▼ and 14: ◆ days of recovery were incubated at 25 °C in incubation buffer containing 5 μM [^{14}C]PAH or 5 μM [^{14}C]TEA for the periods indicated. D-[^{3}H]Mannitol was used to estimate the extracellular trapping and non-specific uptake of [^{14}C]PAH and [^{14}C]TEA. Each point represents the mean ± S.E. for 5–8 slices from different rats. $^{\dagger}P < 0.05$, vs. normal rats. $^{*}P < 0.05$, vs. hyperuricemic rats on day 0.

transport showed a higher correlation with the protein level of rOAT1 than that of rOAT3 (Fig. 6), demonstrating that rOAT1 was a dominant transporter mediating the basolateral uptake of PAH. Basolateral TEA transport showed a high correlation with the protein level of rOCT2 (Fig. 6). As far as we know, this is the first report demonstrating the restoration of renal organic ion transporters (slc22a) during recovery from renal impairment, accompanying the change of basolateral uptake of PAH and TEA in the kidney.

The expression of rOCT2 is regulated by testosterone [19]. In contrast to rOCT2, renal expression of rOAT1 and rOCT1 was not changed between male and female, suggesting little or no contribution of testosterone in the regulation of renal rOAT1 and rOCT1 [22]. In addition, both plasma testosterone levels and the expression levels of rOCT2 decreased in 5/6 nephrectomized rats, where the expression levels of rOCT2 were restored by the administration of physiological concentrations of testosterone [17]. In clinical cases, a lower serum testosterone level was reported to be associated with chronic renal failure [23,24]. In the present study, both rOCT2 expression and plasma testosterone concentration decreased in hyperuricemia, and were restored to normal during recovery from hyperuricemia. However, the correlation between rOCT2 expression and plasma testosterone concentration was not significant. These results suggested that the decreased plasma testosterone level was one of the determinants of rOCT2 expression in hyperuricemic rats.

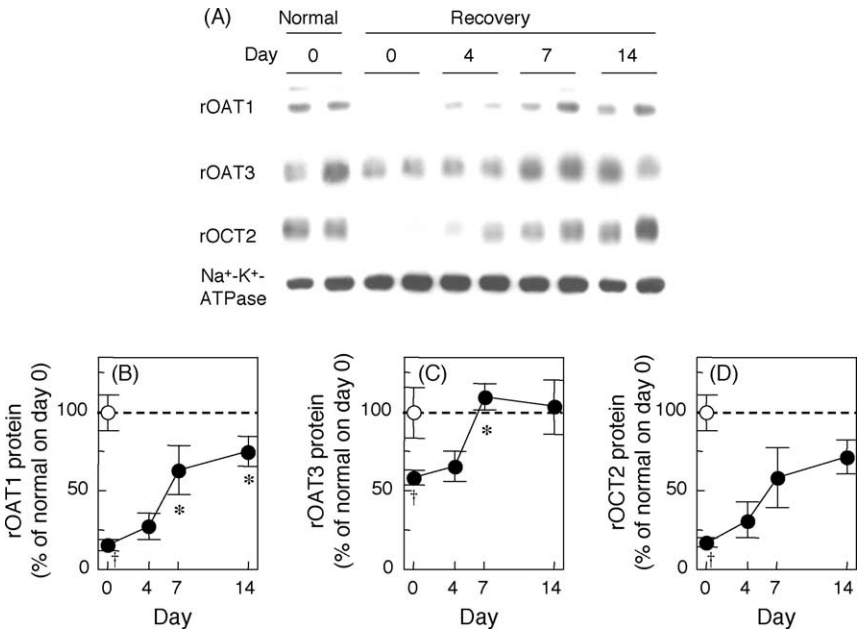

Fig. 4. Western blot analyses of rOAT1, rOAT3 and rOCT2 in crude membrane fractions from the kidneys during recovery from hyperuricemia. Crude membrane fractions from the kidneys of normal and hyperuricemic rats at 0, 4, 7 and 14 days of recovery were separated by SDS-PAGE. rOAT1, rOAT3, rOCT2 and Na^{+}-K^{+}-ATPase α-1 subunit were identified with each antibody. The results in a typical experiment are shown in panel (A). The ratio of rOAT1 (B), rOAT3 (C) and rOCT2 (D) density to Na^{+}-K^{+}-ATPase α-1 subunit density. Each point represents the mean ± S.E. for three normal (○) and four hyperuricemic (●) rats from two experiments. $^{\dagger}P < 0.05$, vs. normal rats. $^{*}P < 0.05$, vs. hyperuricemic rats on day 0.

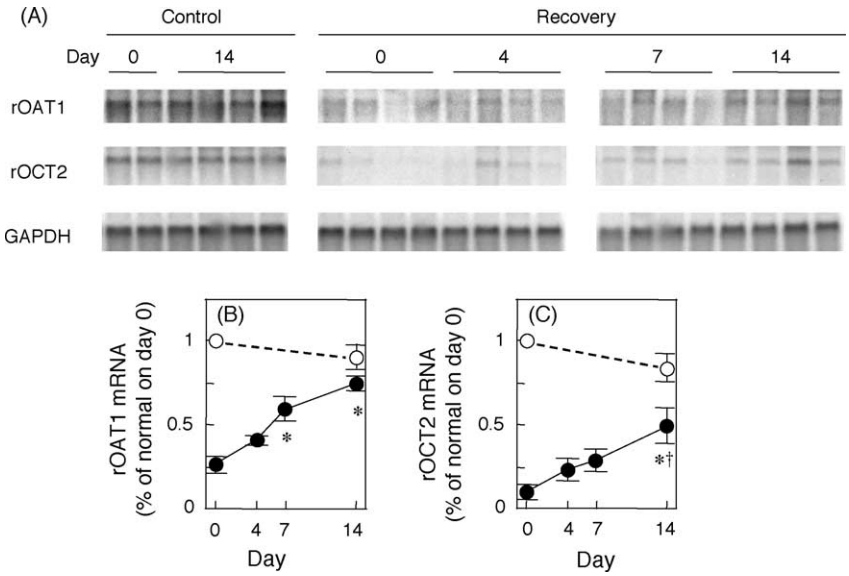

Fig. 5. Northern blot analyses of rOAT1 and rOCT2 during recovery from hyperuricemia. Total RNA (5 μg) from the kidneys of normal and hyperuricemic rats at 0, 4, 7 and 14 days of recovery was hybridized with rOAT1, rOCT2 and GAPDH cDNA probes under high stringency. The results in a typical experiment are shown in panel (A). Densitometry of rOAT1 (B) and rOCT2 (C) mRNAs was corrected for loading with GAPDH mRNA. Each point represents the mean ± S.E. for two to four normal (○) and four hyperuricemic (●) rats. $^{\dagger}P < 0.05$, vs. normal rats. $^{*}P < 0.05$, vs. hyperuricemic rats on day 0.

The dosage regimen of various drugs for patients with renal insufficiency is generally determined according to the value of creatinine clearance. However, renal excretion of ionic drugs into urine is mediated not only by glomerular filtration but also by tubular secretion via organic anion and cation transporters. Actually, the dosage schedule based on creatinine clearance was demonstrated to be inadequate for ampicillin and cephalexin dosing in some patients with renal insufficiency [25]. Recently, we reported that the elimination rate of cefazolin, which is a substrate of hOAT3, was significantly correlated with the levels of hOAT3 mRNA in humans [26]. In the present study, basolateral uptake of PAH and TEA in the kidney was significantly correlated with the expression of rOAT1 and

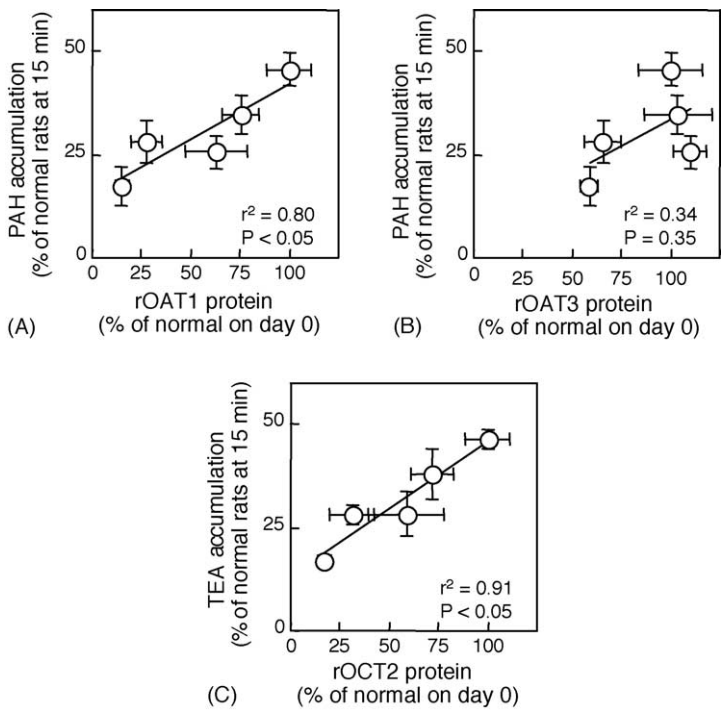

Fig. 6. Correlation between protein levels of rOAT1 (A), rOAT3 (B) and rOCT2 (C) and initial uptake activity of PAH (A and B) and TEA (C) by the renal slices during recovery from hyperuricemia. The linear regression was obtained with the mean values of rOAT1, rOAT3 and rOCT2 at protein levels and initial uptake activity of PAH and TEA. Each point represents the mean ± S.E. obtained in Figs. 3 and 4.

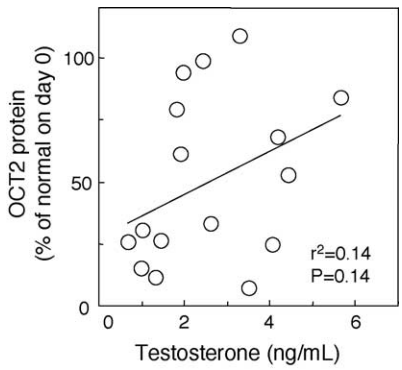

Fig. 7. Correlation between plasma testosterone and rOCT2 protein levels in the kidney during recovery from hyperuricemia. The linear regression was obtained with the plasma concentration of testosterone and rOCT2 protein levels of 17 rats during recovery from hyperuricemia.

rOCT2, respectively. Moreover, the recovery rate of rOAT1, rOAT3 and rOCT2 expression was slower than that of creatinine clearance. Based on these findings, dosage regiments according to the activity of organic anion and cation transport in addition to creatinine clearance should be helpful for precise dosage regimen in the patients with renal dysfunctions.

In conclusion, renal expression of organic ion transporters, rOAT1, rOAT3 and rOCT2, was reversibly regulated by hyperuricemia, accompanying the change of organic ion transport. Although further clinical investigations on the expression levels of drug transporters in several disease states are needed, the expression profiles of drug transporters may be useful information for understanding the alteration of renal drug secretion.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

[1] Pritchard JB, Miller DS. Mechanisms mediating renal secretion of organic anions and cations. Physiol Rev 1993;73:765–96.
[2] Inui K, Masuda S, Saito H. Cellular and molecular aspects of drug transport in the kidney. Kidney Int 2000;58:944–58.
[3] Sekine T, Watanabe N, Hosoyamada M, Kanai Y, Endou H. Expression cloning and characterization of a novel multispecific organic anion transporter. J Biol Chem 1997;272:18526–9.
[4] Sweet DH, Wolff NA, Pritchard JB. Expression cloning and characterization of ROAT1. The basolateral organic anion transporter in rat kidney. J Biol Chem 1997;272:30088–95.
[5] Cha SH, Sekine T, Fukushima J, Kanai Y, Kobayashi Y, Goya T, et al. Identification and characterization of human organic anion transporter 3 expressing predominantly in the kidney. Mol Pharmacol 2001; 59:1277–86.
[6] Sekine T, Cha SH, Endou H. The multispecific organic anion transporter (OAT) family. Pflügers Arch 2000;440:337–50.
[7] Uwai Y, Okuda M, Takami K, Hashimoto Y, Inui K. Functional characterization of the rat multispecific organic anion transporter OAT1 mediating basolateral uptake of anionic drugs in the kidney. FEBS Lett 1998;438:321–4.
[8] Motohashi H, Sakurai Y, Saito H, Masuda S, Urakami Y, Goto M, et al. Gene expression levels and immunolocalization of organic ion transporters in the human kidney. J Am Soc Nephrol 2003;13:866–74.
[9] Gründemann D, Gorboulev V, Gambaryan S, Veyhl M, Koepsell H. Drug excretion mediated by a new prototype of polyspecific transporter. Nature 1994;372:549–52.
[10] Okuda M, Saito H, Urakami Y, Takano M, Inui K. cDNA cloning and functional expression of a novel rat kidney organic cation transporter, OCT2. Biochem Biophys Res Commun 1996;224:500–7.
[11] Koepsell H, Gorboulev V, Arndt P. Molecular pharmacology of organic cation transporters in kidney. J Membr Biol 1999;167:103–17.
[12] Urakami Y, Okuda M, Masuda S, Akazawa M, Saito H, Inui K. Distinct characteristics of organic cation transporters, OCT1 and OCT2, in the basolateral membrane of renal tubules. Pharm Res 2001;18:1528–34.
[13] Habu Y, Yano I, Takeuchi A, Saito H, Okuda M, Fukatsu A, et al. Decreased activity of basolateral organic ion transports in hyperuricemic rat kidney: roles of organic ion transporters, rOAT1, rOAT3 and rOCT2. Biochem Pharmacol 2003;66:1107–14.
[14] Huang Q, Dunn II RT, Jayadev S, DiSorbo O, Pack FD, Farr SB, et al. Assessment of cisplatin-induced nephrotoxicity by microarray technology. Toxicol Sci 2001;63:196–207.
[15] Demeule M, Brossard M, Béliveau R. Cisplatin induces renal expression of P-glycoprotein and canalicular multispecific organic anion transporter. Am J Physiol Renal Physiol 1999;277:F832–40.
[16] Laouari D, Yang R, Veau C, Blanke I, Friedlander G. Two apical multidrug transporters, P-gp and MRP2, are differently altered in chronic renal failure. Am J Physiol Renal Physiol 2001;280:F636–45.
[17] Ji L, Masuda S, Saito H, Inui K. Down-regulation of rat organic cation transporter rOCT2 by 5/6 nephrectomy. Kidney Int 2002;62:514–24.
[18] Brown EA, Kliger AS, Hayslett JP, Finkelstein FO. Renal function in rats with acute medullary injury. Nephron 1980;26:64–8.
[19] Urakami Y, Okuda M, Saito H, Inui K. Hormonal regulation of organic cation transporter OCT2 expression in rat kidney. FEBS Lett 2000;473:173–6.
[20] Iseki K, Oshiro S, Tozawa M, Iseki C, Ikemiya Y, Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res 2001;24:691–7.
[21] Mazaali M, Hughes J, Kim Y-G, Jefferson JA, Kang D-H, Godon KL, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38: 1101–1106.
[22] Urakami Y, Nakamura N, Takahashi K, Okuda M, Saito H, Hashimoto Y, et al. Gender differences in expression of organic cation transporter OCT2 in rat kidney. FEBS Lett 1999;461:339–42.
[23] Joven J, Villabona C, Rubies-Prat J, Espinel E, Galard R. Hormonal profile and serum zinc levels in uraemic men with gonadal dysfunction undergoing haemodialysis. Clin Chim Acta 1985;148:239–45.
[24] Mitchell R, Bauerfeld C, Schaefer F, Scharer K, Rovertson WR. Less acidic forms of luteinizing hormone are associated with lower testosterone secretion in men on haemodialysis treatment. Clin Endocrinol 1994;41:65–73.
[25] Hori R, Okumura K, Kamiya A, Nihira H, Nakano H. Ampicillin and cephalexin in renal insufficiency. Clin Pharmacol Ther 1983;34: 792–8.
[26] Sakurai Y, Motohashi H, Ueo H, Masuda S, Saito H, Okuda M, et al. Expression levels of renal organic anion transporters (OATs) and their correlation with anionic drug excretion in patients with renal diseases. Pharm Res 2004;21:61–7.