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Involvement of the Renal Kallikrein-Kinin System in Furosemide-Induced Natriuresis in Rats

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ABSTRACT—This study examined whether the renal kallikrein-kinin system (KKS) is involved with furosemide-induced natriuresis in rats. Intravenous administration of furosemide (10 mg/kg) to anesthetized rats infused with physiological saline (saline) increased renal KK excretion as well as urine volume and urinary excretions of sodium, chloride and potassium. The change in the increase of renal KK excretion by furosemide at a dose of 1.0 mg/kg relative to the control was larger than that of urine volume. Pretreatment with a B_2-receptor antagonist, 8-[3-[*N*-[(*E*)-3-(6-acetamidopyridin-3-yl)acryloylglycyl]-*N*-methylamino]-2,6-dichlorobenzyloxy]-2-methylquinoline (FR173657, 100 mg/kg), significantly inhibited the furosemide-induced natriuresis by 58.6%. The effect of FR173657 on the furosemide-induced natriuresis was also examined in hypotonic saline-loading rats. Similar to the saline-loading rats, urinary excretion of sodium collected during the first 8 h in metabolic cages significantly reduced by 22.4% when FR173657 (100 mg/kg) was given concurrently with furosemide (100 mg/kg) and hypotonic saline (5% of body wt.). These results indicate that furosemide increased renal KK excretion through a mechanism different from a washout mechanism and induced natriuresis partly through an augmentation of the renal KKS following the increase in renal KK excretion in both the saline- and hypotonic saline-loading rats.

Keywords: B_2-receptor antagonist, FR173657, Furosemide, Natriuresis, Renal kallikrein

Furosemide, a loop diuretic, is known to prevent sodium reabsorption through an inhibition of Na^+-K^+-$2Cl^-$ transporter at the ascending loops of Henle, while it has been reported that furosemide also affects on the renal kallikrein-kinin system (KKS) (1). Renal kallikrein (KK) is considered to liberate kinins from low-molecular weight kininogens (2) and kinins bind to B_2 receptors present in the collecting tubule to induce inhibition of reabsorption of sodium and water (3 – 5). Transient increases in urinary excretion of KK or kinin by furosemide have been reported in rat and human studies (6 – 10).

In a recent report, the B_2-receptor antaganist D-Arg [Hyp^3, Thi^5, D-Tic^7, Oic^8]-bradykinin (Hoe140) was shown to blunt the diuretic and natriuretic effects of furosemide in deoxycorticosterone-treated rats, but not in vehicle-treated rats (11). It has been reported that the level of mineralcorticoid activity influenced the furosemide-induced increase in renal KK secretion, which decreased in adrenalectomized rats and increased in deoxycorticosterone acetate (DOCA)-treated adrenalectomized rats (12). Accordingly, the furosemide-induced natriuresis and diuresis might be mediated by the renal KKS when the renal KK secretion is increased, which may cause an activation of the renal KKS.

FR173657, another B_2-receptor antagonist, is an orally active non-peptide compound (13). Oral administration of FR173657 (30 mg/kg) 1 h before injection of bradykinin or carrageenin inhibited plasma exudation in rat pleurisy models, and the inhibitory effect of FR173657 on plasma exudation persisted for more than 4 h (14). In this study, changes in urinary KK excretion, urine volume, and urinary excretion of sodium, chloride and potassium after administration of furosemide were examined in rats infused with physiological saline (saline). In addition, the effect of FR173657 on the furosemide-induced diuresis and natriuresis were investigated in rats that received saline intravenously or hypotonic saline by gavage.

MATERIALS AND METHODS

Materials

Male Sprague-Dawley rats (specific pathogen-free, 8- to

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10-week-old; Shizuoka Laboratory Animal Center, Hamamatsu) were used. All rats were given normal rat chow and tap water ad libitum; and they were housed at constant humidity (60 ± 5%) and temperature (25 ± 1°C) and kept on a continuous 12-h light / 12-h dark cycle. This study was performed in accordance with the Kitasato University School of Medicine guidelines for animal experiments.

Furosemide was from Hoechst Marion Roussel Pharmaceuticals, Inc. (Tokyo). 8-[3-[*N*-[(*E*)-3-(6-Acetamidopyridin-3-yl)acryloylglycyl]-*N*-methylamino]-2,6-dichlorobenzyloxy]-2-methylquinoline (FR173657; Fujisawa Pharmaceutical Co., Ltd., Osaka) was suspended at a concentration of 100 mg/ml in 0.5% gum arabic (Wako Pure Chemical Industries, Ltd., Osaka).

Experimental procedures in saline-loading rats under anesthetization

Rats were initially anesthetized with 50 mg/kg pentobarbital sodium intraperitoneally (Nembutal; Abbott Lab., North Chicago, IL, USA). Part of the trachea was separated from the surrounding tissue, and a polyethylene cannula (PE-100; Clay Adams, Parsippany, NJ, USA) was placed under the separated trachea. A tracheostomy was then performed. The urinary bladder was cannulated through a small abdominal incision using a polyethylene cannula (PE-50, Clay Adams). The left femoral vein was cannulated with a polyethylene cannula (PE-10, Clay Adams) for infusion. Body temperature was measured continuously with a thermometer (Model CTM-303; Terumo, Tokyo) and maintained at 37.5 ± 0.5°C with a desk lamp and heated table. All rats were infused continuously using an infusion pump (Model 235; Atom, Tokyo) to deliver physiological saline (saline) containing 0.4% pentobarbital sodium through the femoral vein at a rate of 6 ml/kg per hour. After these conditions were maintained for 30 min, collections of urine were performed every 15 min and placed on ice.

Sixty minutes after the start of infusion, 300 μl of furosemide at doses of 0.1 mg/kg (n = 8), 1 mg/kg (n = 8) or 10 mg/kg (n = 6) was given as a bolus i.v. injection. Control animals were administered 300 μl of saline (n = 7). The infusion was then performed for a further 45 min after the injection of furosemide at a dose of 10 mg/kg. After the administration of lower doses of furosemide, the infusion was continued for 15 min.

In the experiment in which the effects of the B_2-receptor antagonist on furosemide-induced increase in urine volume and urinary excretion of sodium, chloride and potassium were examined, FR173657 at a dose of 100 mg/kg, which was a sufficient dose judging from the inhibition of plasma exudaion by FR173657 in rat pleurisy models (14), was administered by gavage at the start of infusion. Sixty minutes later, 300 μl of furosemide at a dose of 10 mg/kg (n = 4) was injected intravenously and then the infusion was performed for 45 min.

Experimental procedures in hypotonic saline-loading rats using metabolic cages

Rats were placed in individual metabolic cages for 8-h urine collection. They were deprived of chow and water. After the collection of the first 8-h urine samples, rats were given FR173657 at a dose of 100 mg/kg followed by 75 mM NaCl solution (5 ml/100 g of body wt.) containing furosemide at a concentration of 2 mg/ml, by gavage; and then the animals were returned to the metabolic cages immediately. Control animals were administered 5% gum arabic solution followed by furosemide solution. The 8-h urine samples from the individual rats were collected repeatedly for 16 h without giving chow and water. Urine volume was noted at the end of the every 8-h period.

Measurement of urinary KK activity

KK activity in the collected urine was measured using a peptidyl fluorogenic substrate for glandular KK, Pro-Phe-Arg-methyl-coumarinylamide (Pro-Phe-Arg-MCA; Peptide Institute, Minoh) (15). A portion of the urine was diluted tenfold with 0.2 M Tris-HCl buffer (pH 7.8). Then 10 μl of the diluted urine was mixed with either 10 μl of soy bean trypsin inhibitor (SBTI; Worthington Biochem., Corp., Halls Mill Road, NJ, USA), an inhibitor of glandular KK, or aprotinin (Wako Pure Chemical Industries), an inhibitor of both glandular and plasma KK, to a final concentration of 0.5 μg/μl. MCA diluted with 0.05 M Tris-HCl buffer containing 0.1 M NaCl and 0.01 M $CaCl_2$ (pH 8.0) was added to either the mixed urine solution or 500 μl of the perfusate to attain a final concentration of 0.05 mM. The reaction mixture was incubated at 37°C for either 10 min or 30 min. After the incubation, 2.0 ml of 17% acetic acid was added to the incubation mixure to stop the reaction, and the fluorescence intensity of the incubation mixure was measured by a fluorescence spectrophotometer (M850; Hitachi, Ltd., Tokyo) (excitation: 380 nm and emission: 460 nm). One unit was defined as the amount of renal KK that released 1 μmol of 7-amino-4-methylcoumarin (Peptide Institute) for 10 min per 1 μl of urine at 37°C. Urinary KK activity was expressed as units (U).

Measurement of urine volume and urinary excretion of sodium, chloride and potassium

Urine volume was determined gravimetrically. To measure urinary excretion of sodium, potassium and chloride, a portion of the urine was diluted tenfold with distilled water. The measurement was performed with ion-selective electrodes (Fuji Dri-Chem Slide Na-K-Cl, Fuji Dri-Chem 800V; Fuji Film Co., Ltd., Tokyo). Urine volume and excreted electrolytes were expressed in μl/15 min per 100 g

body wt. and μmol/15 min per 100 g body wt., respectively.

Data analysis

Values are expressed as the mean ± S.E.M. Statistical analysis of comparative values was performed using the unpaired *t*-test. Significance levels of the dose-response increases in urinary KK excretion by furosemide were estimated by one-factor ANOVA followed by Scheffe's F multiple comparison. The differences with a probability less than 5% were considered to be significant ($P<0.05$).

RESULTS

Changes in urinary KK excretion, urine volume and urinary excretion of sodium, chloride and potassium

Effect of furosemide administration on urinary KK excretion, urine volume and urinary excretion of sodium, potassium and chloride were examined in anesthetized rats. As shown in Fig. 1a, urinary KK activity significantly increased 15 min after administration of furosemide (154.5 ± 21.5 mU/15 min per 100 g body wt.) compared with the control (15.5 ± 1.5 mU/15 min per 100 g body wt.) and

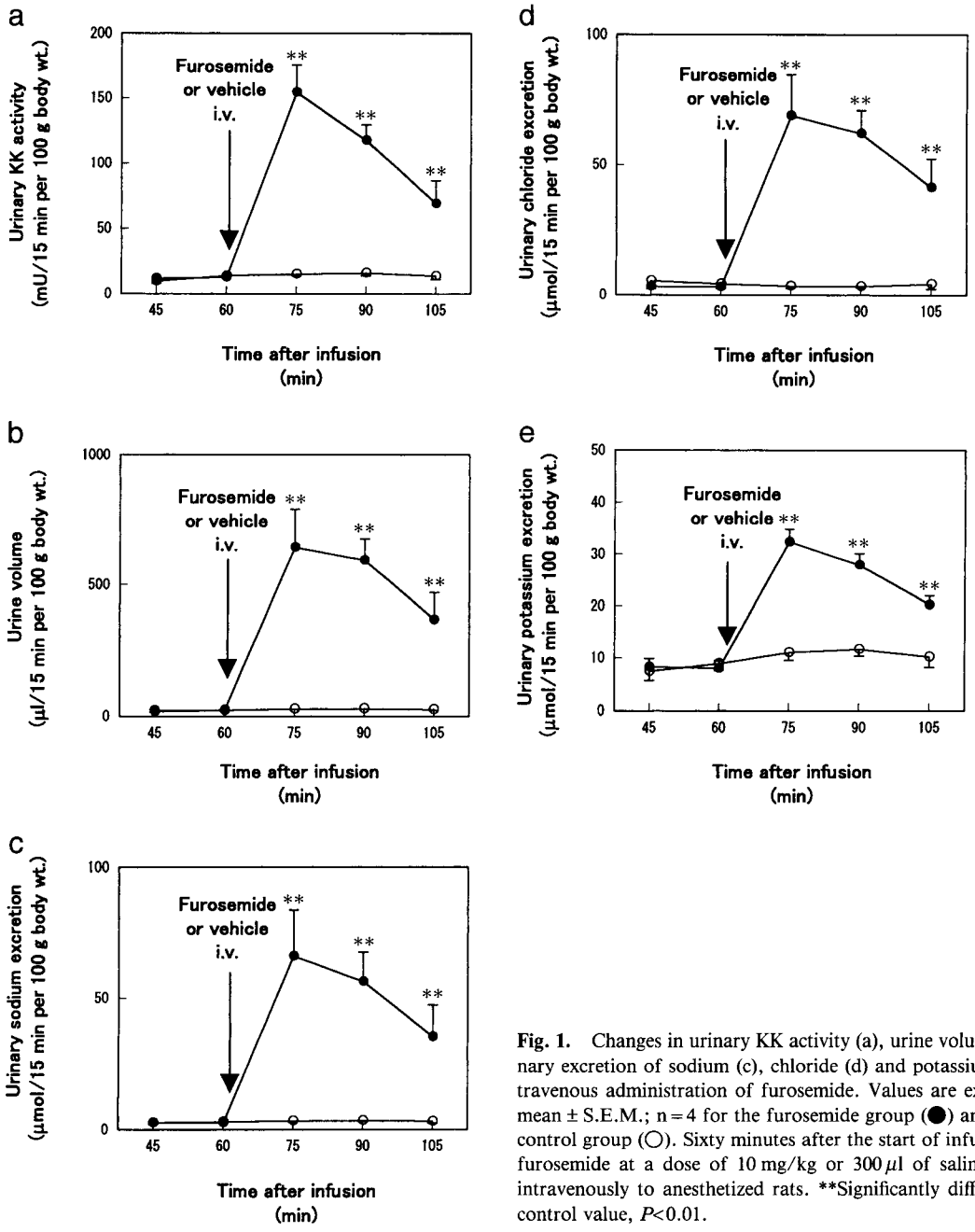

Fig. 1. Changes in urinary KK activity (a), urine volume (b) and urinary excretion of sodium (c), chloride (d) and potassium (e) after intravenous administration of furosemide. Values are expressed as the mean ± S.E.M.; n = 4 for the furosemide group (●) and n = 7 for the control group (○). Sixty minutes after the start of infusion, 300 μl of furosemide at a dose of 10 mg/kg or 300 μl of saline was injected intravenously to anesthetized rats. **Significantly different from the control value, $P<0.01$.

decreased gradually during a further 30 min. Similar time course patterns of the increases in urine volume and urinary excretions of sodium, chloride and potassium were observed (Fig. 1: b – e).

Dose-dependent increases of urinary KK excretion and urine volume due to furosemide

Several doses of furosemide were administered to determine whether urinary KK excretion increased dose-dependently or increased in parallel with an increase in urine volume. Figure 2 shows the increases in urinary KK excretion and urine volume relative to the control values. Furosemide increased renal KK excretion in a dose-dependent manner. The change in the relative increase of renal KK excretion by furosemide at a dose of 1.0 mg/kg (198.9 ± 27.4) was significantly larger than that of urine volume (108.3 ± 21.3).

Effect of FR173657 on the furosemide-induced increases in urine volume and urinary excretions of sodium, chloride and potassium

To examine whether the renal KKS is involved with the furosemide-induced diuresis and natriuresis, effect of FR173657 on these factors were investigated. In saline-loading rats receiving vehicle solution, urine volume (442.7 ± 125.2 μl/15 min per 100 g body wt.) and urinary excretion of sodium (42.5 ± 13.7 μmol per 15 min/100 g body wt.), chloride (45.6 ± 13.0 μmol/15 min per 100 g body wt.), and potassium (15.7 ± 2.8 μmol/15 min per 100 g body wt.) peaked 15 min after administration of furosemide (Fig. 3), similar to the results shown in Fig. 1. Pretreatment with FR173657 did not affect the increase in urinary excretion of potassium (Fig. 3d). Increases in urine volume and urinary excretions of sodium and chloride 15 min after administration of furosemide were inhibited by 48%, 59% and 51%, respectively, after the pretreatment with FR173657 compared with the vehicle treatment, and the inhibition of the increase in urinary excretion of sodium was significant (Fig. 3: a – c).

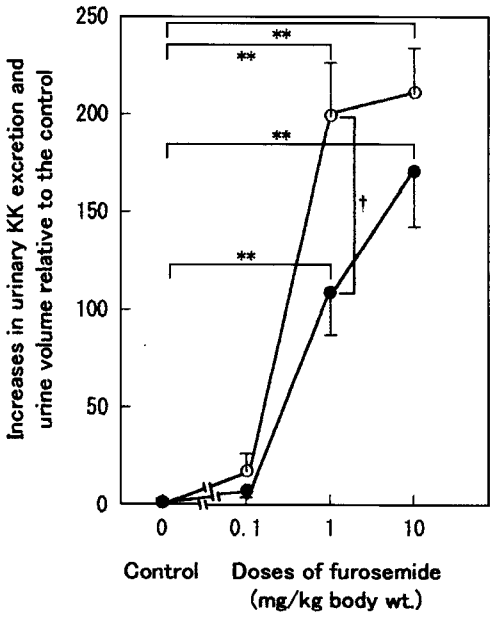

Fig. 2. Increases in urinary KK excretion (○) and urine volume (●) during 15 min after administration of furosemide relative to the control. Values are expressed as the mean ± S.E.M.; n = 7 for the control group, n = 8 for furosemide at doses of 0.1 and 1 mg/kg, and n = 6 for furosemide at a dose of 10 mg/kg. Furosemide or vehicle was administered 60 min after the start of infusion. **Significantly different from the control value, $P<0.01$; †Significantly different from corresponding value, $P<0.05$.

In the rats that were kept in the metabolic cages without supply of water and food, urine volume and urinary excretions of sodium, chloride and potassium were 1.20 ± 0.12 ml/8 h per 100 g body wt. and 0.20 ± 0.03, 0.20 ± 0.02 and 0.22 ± 0.02 mmol/8 h per 100 g body wt., respectively. Increases in urine volume and urinary excretions of sodium, chloride and potassium were expressed as values relative to those before administration of furosemide with hypotonic saline in Fig. 4. Furosemide together with loading of hypotonic saline caused marked increases in these parameters (urine volume: 7.4 ± 0.3 and urinary excretions of sodium: 4.9 ± 0.3, chloride: 4.4 ± 0.2 and potassium: 2.0 ± 0.1 times). Pretreatment with FR173657 blunted the increases of these parameters significantly except urine volume (urine volume: 7.8 ± 0.4 and urinary excretions of sodium: 3.8 ± 0.2, chloride: 3.5 ± 0.2 and potassium: 1.6 ± 0.1 times).

DISCUSSION

In the present experiments, renal KK as well as urine volume and urinary excretions of sodium, chloride and potassium increased 15 min after administration of furosemide in the saline-loading rats (Fig. 1). FR173657 inhibited more than half of the furosemide-induced increase in urinary excretion of sodium compared with the control (Fig. 3). FR173657 is considered to have no nonspecific action to Na^+-K^+-$2Cl^-$ cotransporter, as urinary excretions of sodium, potassium and chloride did not change 45 and 60 min after administration of FR173657 compared with that of vehicle (Fig. 3). A similar result was shown in hypotonic-saline loading rats that FR173657 inhibited natriuresis by 22.4% 8 h after administration of furosemide compared with the control (Fig. 4). These results are partly consistent with the previous report, in which Hoe140 (300 μg/kg, s.c.) suppressed the diuretic and natriuretic effects of furosemide by 41.5% and 36.0% in rats pretreated with deoxycorticosterone enantate, an aldosterone derivative, weekly for two weeks (25 mg/kg, s.c.) (11). In these rats, renal KK secretion could increase as

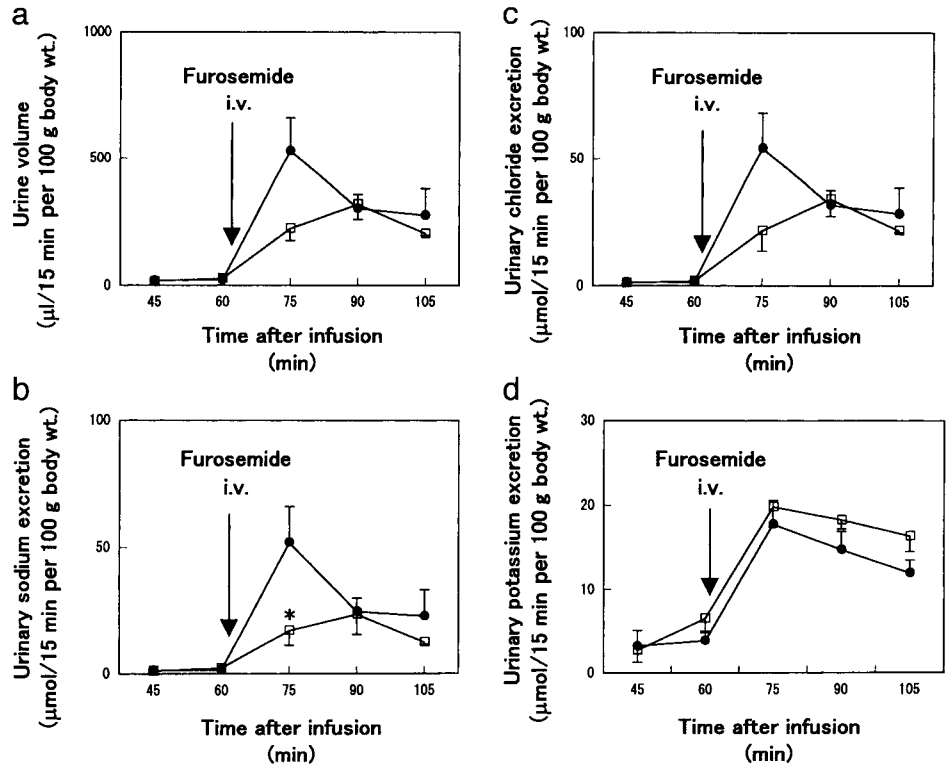

Fig. 3. Effect of the B_2-receptor antagonist FR173657 on the furosemide-induced increases in urine volume (a) and urinary excretion of sodium (b), chloride (c) and potassium (d). Values are expressed as the mean ± S.E.M.; n = 4 for FR173657-pretreated (□) and vehicle-pretreated (●) groups. FR173657 at a dose of 100 mg/kg or 5% gum arabic solution was given by gavage at the start of infusion, and 60 min later, 300 μl of furosemide at a dose of 10 mg/kg was injected intravenously to anesthetized rats. *Significantly different from the control value, $P<0.05$.

aldosterone is a secretagogue of renal KK secretion (16, 17), and the uninephrectomized rats that received deoxycorticosterone acetate weekly for three weeks (5 mg/kg, s.c.) showed an increase in urinary excretion of active KK that was 3.2 times more than the pre-treated rats (18). In the present study, the increase in renal KK secretion was 12-fold higher in the saline-loading rats (Fig. 1a), whereas, it was only 2.8 fold higher in the hypotonic-saline loading rats (data not shown) after administration of furosemide. Differences in potency of the inhibitory effects on the furosemide-induced natriuresis by FR173657 or Hoe140 might be attributed to differences in the increases in renal KK secretion which lead to an activation of the renal KKS. Our previous study using kininogen-deficient rats revealed that the renal KKS accelerates urinary excretion of sodium when a non-pressor dose of sodium chloride or angiotensin II was administered to rats (19, 20). The inhibitory effect on the furosemide-induced diuresis and natriuresis by Hoe 140 was not found in vehicle-treated rats (11), which means that the furosemide-induced natriuresis and diuresis were not involved with the renal KKS under physiological conditions. It was also shown in our preliminary study using kininogen-deficient rats that natriuresis was inhibited by 25% and 52% 8 h after administration of furosemide at doses of 10 mg/kg and 30 mg/kg, respectively, compared with normal rats from the same strain (Y. Ikeda et al., unpublished data).

FR173657 did not have an inhibitory effect on the increase in urinary excretion of potassium by furosemide (Fig. 3), and this result was explained by the report in which bradykinin caused an inhibition of net sodium absorption without affecting potassium secretion in the cortical collecting duct of rats treated with deoxycorticosterone pivalate (5 mg, i.m.) for 7 – 12 days (4). On the other hand, the furosemide-induced increase in urinary excretion of potassium was inhibited by treatment with FR173657 in the hypotonic saline-loading rats (Fig. 4). It is reported that intravenous infusion of Hoe140 decreases urine flow rate in rat medullary collecting duct using the microcatheterization technique (21). Thus, it is possible that urinary excretion of potassiumwas inhibited by FR173657 as a result of a reduction in the rate of fluid delivery to the distal nephron followed by a decrease in urinary potassium excretion at the distal tubule (22). This result was only observed in the hypotonic saline-loading rats, which might be due to the differences in the route of administration and the ex-

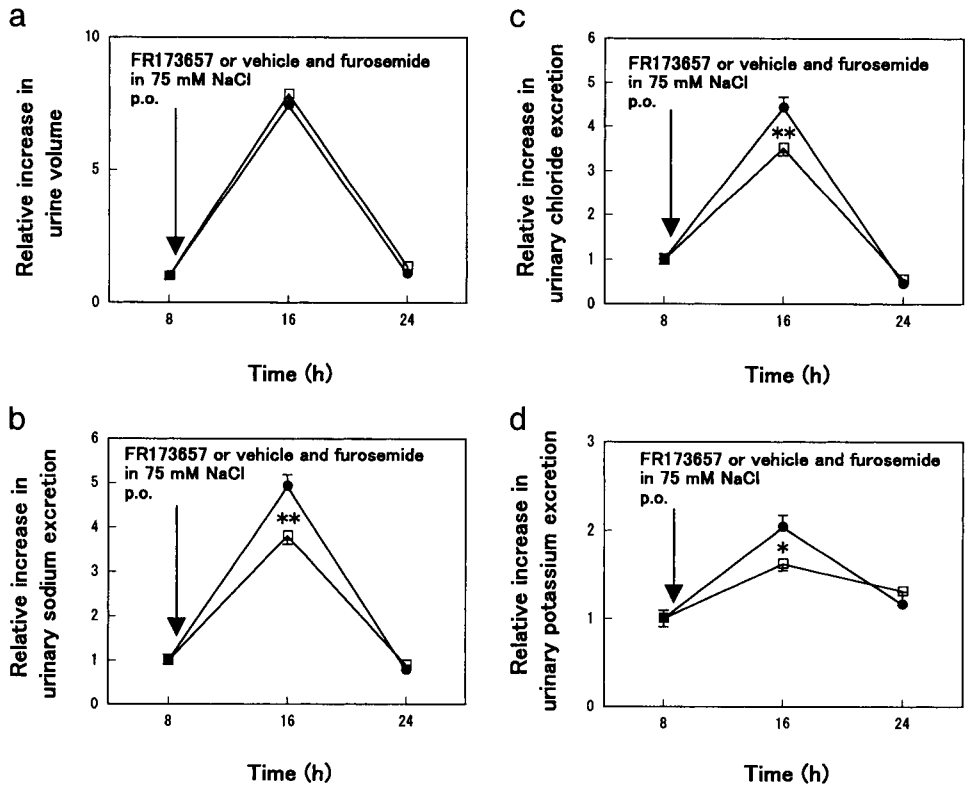

Fig. 4. Effect of the B_2-receptor antagonist FR173657 on the furosemide-induced increases in urine volume (a) and urinary excretion of sodium (b), chloride (c) and potassium (d) in hypotonic saline-loading rats. Values are expressed as the mean ± S.E.M; n = 8 for FR173657-pretreated (□) and vehicle-pretreated (●) groups. Eight hours after the collection of urine from metabolic cages, FR173657 at a dose of 100 mg/kg or 5% gum arabic solution was given concurrently with furosemide at a dose of 100 mg/kg and hypotonic saline (5% of body wt.) by gavage. Urine was collected for another 16 h at an 8-h interval. *, **Significantly different from the control value, $P<0.05$, $P<0.01$, respectively.

perimental time course compared with the saline-loading rats.

Mechanisms for the increase in renal KK secretion by furosemide still remain unclear. It has been considered so far that the washout phenomenon is a major mechanism of the furosemide-induced increase in renal KK secretion (23). According to our preliminary results, renal KK excretion increased in parallel with urine volume after volume loading, an intravenous infusion with saline at a rate of 60 ml/kg per hour (T. Fujita et al., unpublished data). The present study showed that the furosemide-induced changes in the augmentation of renal KK excretion were larger than those of diuresis (Fig. 2). Additionally, Obika and Marin-Grez (12) reported that the furosemide-induced increase in renal KK secretion did not appear to be a washout of the enzyme, as repeated injections of furosemide caused a consistent increase in urinary KK excretion in rats. Therefore, it is suggested that furosemide could increase renal KK excretion via a mechanism different from a washed one. However, furosemide is unlikely to be involved in the increase of renal KK secretion through a direct action on the connecting tubule cells, as Na^+-K^+-$2Cl^-$ cotransporter was not observed in the connecting tubule cells where renal KK is localized (24), but shown on the basolateral membrane of renal cortical collecting duct, that of intercalated cells of outer and inner medullary collecting ducts, and glomerular elements in the immunofluorescence study (25). We previously reported (26) that superfusion with a high concentration of potassium solution to sliced kidney cortices increased renal KK secretion in rats. The increase in urinary potassium excretion induced by furosemide may contribute to the increase in renal KK excretion.

The present study showed that the furosemide-induced natriuresis was involved with the renal KKS in the saline- and hypotonic saline-loading rats in which renal KK secretion was augmented. We previously reported (27) that the renal KKS blunts the development of hypertension through natriuresis in animal models. Elucidation of mechanisms responsible for regulation of the renal KKS by furosemide is expected to be an important step in the development of new anti-hypertensive drugs.

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