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ORIGINAL PAPER

Renal response to anaphylaxis in anesthetized rats and isolated perfused rat kidneys: roles of nitric oxide

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Abstract

We determined the renal responses to anaphylaxis and the effects of a nitric oxide synthesis inhibitor, L-NAME, in anesthetized rats and isolated perfused rat kidneys. After the ovalbumin antigen injection, the sensitized rats showed transient and substantial decreases in mean blood pressure and renal blood flow and an increase in renal vascular resistance. Creatinine clearance, a measure of renal function, decreased to 53% baseline at 2 h after antigen. L-NAME pretreatment significantly enhanced the antigen-induced renal vasoconstriction and renal dysfunction. Moreover, plasma creatinine levels significantly increased only in the L-NAME pretreated rats. Separately, in isolated perfused kidneys, we observed the antigen-induced renal vasoconstriction and its augmentation by L-NAME. In conclusion, the renal vascular response to the antigen is vasoconstriction, which is enhanced by L-NAME in both isolated perfused rat kidneys and anesthetized rats; it is accompanied by renal dysfunction, which is also augmented by L-NAME.

Keywords Anaphylactic shock · Anesthetized rats · Perfused rat kidney · Renal vasoconstriction · Renal dysfunction · L-NAME

Introduction

Anaphylactic shock triggered by an allergic reaction is potentially life threatening [1]. Anaphylactic hypotension is characterized by vasodilatation, which may accompany increased blood flow to an affected region. Actually, in the anaphylactic shock models of anesthetized rats, the blood flow transiently increases in the mesenteric artery [2], hepatic artery [3], femoral artery [4], and gastric artery [5]. In contrast, the blood flow of the common carotid artery, which mainly supplies the brain, dose not increase, suggesting the absence of vasodilatation, in the same rat model [6]. Regional differences in the vascular responses to anaphylaxis may exist. However, the renal homodynamic response to anaphylaxis has not been reported in anesthetized rats, although the perfused kidneys isolated from the sensitized rats showed vasoconstrictor response to the antigen [7]. Therefore, the first aim of this study was to determine the changes in the renal vascular resistance (RVR) in anesthetized rats during systemic anaphylactic hypotension, as well as those in the isolated perfused sensitized rat kidneys exposed to the antigen.

It is reported that nitric oxide (NO) plays a major role in anaphylactic hypotension of anesthetized dogs, mice and rats [8–10]. Moreover, in response to the antigen, NO is endogenously released in the sensitized rat derived isolated pulmonary [11–13] and mesenteric arteries [14], coronary artery of the isolated heart [15, 16], and portal vein of the isolated liver [17, 18]; L-NAME enhances anaphylactic vasoconstriction of pulmonary artery, coronary artery, and mesenteric artery, and venoconstriction of portal veins. However, it is not known how L-NAME affects renal vessels during anaphylaxis in anesthetized rats or isolated perfused rat kidneys. Therefore, the second aim of this study was to determine roles of NO in the renal hemodynamic response to the antigen in anesthetized sensitized rats and perfused sensitized rat kidneys by measuring continuously renal blood flow and renal arterial and venous pressures.

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Finally, renal dysfunction is sometimes observed in patients suffering from anaphylactic shock [19]. However, it remains unknown whether the glomerular filtration rate (GFR), an index of renal function, could decrease in an experimental model of systemic anaphylaxis. On the other hand, L-NAME induces an increase in GFR in rats, which may be ascribed to predominant constriction of rat post-glomerular vessels [20–22], resulting in elevation of the filtration pressure. However, modulation of renal function by L-NAME is not known during systemic anaphylaxis. Thus, the third aim was to measure GFR during anaphylactic hypotension by assessing creatinine clearance in anesthetized rats.

Materials and methods

Animal and sensitization

Fifty-two male Sprague–Dawley rats (Japan SLC, Shizuoka, Japan) weighing 411 ± 7 g were used and maintained at 23 °C and under pathogen-free conditions on a 12:12-h dark/light cycle and allowed food and water ad libitum. The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University (2016-52). Rats were actively sensitized by the subcutaneous injection of an emulsion made by mixing equal volumes of complete Freund's adjuvant (0.5 ml) and 0.5 mg ovalbumin (grade V, Sigma), as previously reported [5]. Two weeks after sensitization, the rats were used for the following experiments. Non-sensitized rats were injected with completed Freund's adjuvant with saline.

In vivo experiment

The sensitized rats were anesthetized with urethane (1.2 g/kg, i.p.) and the left carotid artery was catheterized with a polyethylene tube to measure mean arterial blood pressure (MBP). The right and left femoral veins were also catheterized for a continuous infusion of saline (10 ml/kg/h) and an injection of the antigen and for measurement of the renal venous pressure (RVP), respectively. After a retroperitoneal incision, a pulsed Doppler flow probe (MC1PRB, Transonic Systems, Ithaca, NY, USA) was placed on the left renal artery to measure the mean renal blood flow (RBF). For measurement of the urinary flow and creatinine clearance, the left urinary duct was catheterized with a polyethylene tube to collect urine drop by drop in a tube suspended from the force transducer (SB-1T, Nihon-Kohden, Tokyo, Japan) and its weight was cumulatively measured. The MBP and RVP were continuously measured with pressure transducers (TP-400T, Nihon-Kohden), and the reference level was set at the level of the right atrium. The renal vascular resistance (RVR) was calculated by the following equation: RVR = (MBP − RVP)/RBF. The vascular pressures, heart rate, and urine weight as well as RVR were digitally recorded at 40 Hz by PowerLab (AD Instruments, Castle Hill, Australia).

The rats were assigned to the following four groups (n = 7/each group): the L-NAME anaphylaxis, D-NAME anaphylaxis, L-NAME control and D-NAME control groups. In the L-NAME groups and D-NAME groups, 10 min after an injection of L-NAME (10 mg/kg; 100 µl, i.v.) and D-NAME (10 mg/kg; 100 µl, i.v.), respectively, the antigen (0.6 mg) was intravenously injected into the sensitized and non-sensitized rats. The rats were observed for 120 min after antigen injection. Creatinine clearance was determined before and 120 min after antigen injection by measuring creatinine concentrations of the serum and urine with the Jaffe method (Wako, Osaka, Japan) [23].

Isolated perfused kidney experiment

The sensitized rats were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). At 5 min after intra-arterial heparinization (500 U/kg) following catheterization of the right carotid artery and laparotomy, the right renal artery was catheterized via the superior mesenteric artery with a stainless-steel catheter (19 G) and then, renal perfusion was begun with the 5% bovine albumin (Sigma-Aldrich Co, St Louis, MO, USA) in Krebs solution (118 mM NaCl, 5.9 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.2 mM NaH_2PO_4, 25.5 mM $NaHCO_3$, and 5.6 mM glucose). Then, the inferior vena cave was catheterized just beneath the right renal vein to obtain the outflow pathway following its ligation above the right renal vein. The right kidney was excised and put in the bath in which warm saline (37 °C) was continuously perfused. The isolated kidney was perfused with the albumin-Krebs solution (50 ml) that was pumped using a Masterflex roller pump from the reservoir through a heat exchanger (37 °C) in a recirculating manner at a constant flow rate so as to obtain the baseline renal arterial blood pressure (RBP) of 78 ± 6 mmHg. The perfusate was oxygenated in the reservoir by continuous bubbling with 95% O_2 and 5% CO_2 (perfusate PO_2 = 300 mmHg). The RBP and RVP were measured using pressure transducers (TP-400T, Nihon-Kohden) attached by sidearm to the appropriate cannulas with the reference points at the kidney pelvis. Renal blood flow rate (Q) was measured with an electromagnetic flow meter (MFV 1200, Nihon-Kohden), and the flow probe

was positioned in the inflow line. RVR was calculated by the following equation: RVR = (RBP − RVP)/Q. RBP, RVP, Q and RVR were continuously recorded at 40 Hz by PowerLab.

Hemodynamic parameters were observed at least for 20 min after the start of perfusion until a stable state was obtained by adjusting Q and the height of the reservoir to a RVP of 0.5 ± 0.2 mmHg and a Q of 6.1 ± 1.3 ml/min/g. After the baseline measurements, the perfused kidneys excised from the sensitized and non-sensitized rats were randomly assigned to four groups, as for the in vivo experiments (n = 6/each group). At 20 min after an injection of L-NAME (100 μM) or D-NAME (100 μM), the antigen (2 mg) was injected into the reservoir.

Statistics

All results are expressed as the mean ± SEM. Data were analyzed by one- and two-way analysis of variance, using repeated-measures for two-way comparison within groups. Comparisons of individual points between groups and within groups were made by Tukey and Dunnett test, respectively. Differences were considered as statistically significant at P values less than 0.05.

Results

In vivo experiment

Figures 1 and 2 show a representative example of the responses of the hemodynamic variables and urine flow to antigen in the D-NAME anaphylaxis and L-NAME anaphylaxis groups, respectively. Figure 3 shows the summary data of time course changes in MBP, RBF, and RVR of all four groups of anesthetized rats. In the D-NAME anaphylaxis group, MBP rapidly decreased from the baseline of 95 ± 4 mmHg to the nadir of 53 ± 1 mmHg at 6 min after antigen, followed by a gradual recovery to 108 ± 6 mmHg at 65 min (Fig. 3a). RBF at 0.5 min after antigen injection did not change significantly, although it increased in accordance with the start of rapid MBP fall in three rats, but not in the other four rats (Fig. 3b). Then, RBF progressively decreased from the baseline of 4.1 ± 0.3 ml/min to a nadir of 0.5 ± 0.1 ml/min at 6 min, followed by a gradual recovery to the levels which were not significantly different from the baseline at 65 min (Fig. 3b). Consequently, RVR significantly increased from the baseline of 24 ± 3 mmHg min/ml to the peak of 116 ± 17 mmHg min/ml (4.8-fold baseline) at 6 min, followed by a return to the levels of the baseline at 25 min (Fig. 3c). On the other hand, any parameters studied did not change significantly throughout the experimental period in the D-NAME control group (Fig. 3).

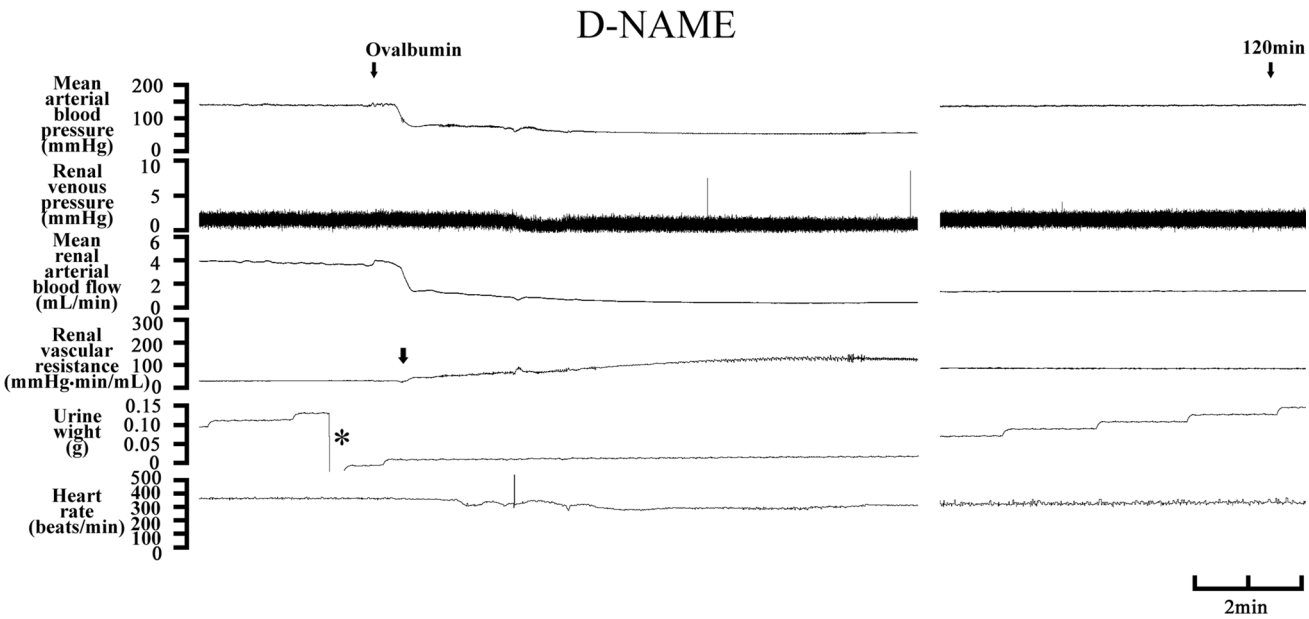

Fig. 1 Representative recordings of the responses of the variables to ovalbumin antigen (0.6 mg) in an anesthetized rat of the D-NAME anaphylaxis group. The *asterisk* indicates the artifact caused by the change of the urine collecting bottle. The *arrow* indicates the absence of a decrease in renal vascular resistance, as indicated in Fig. 2

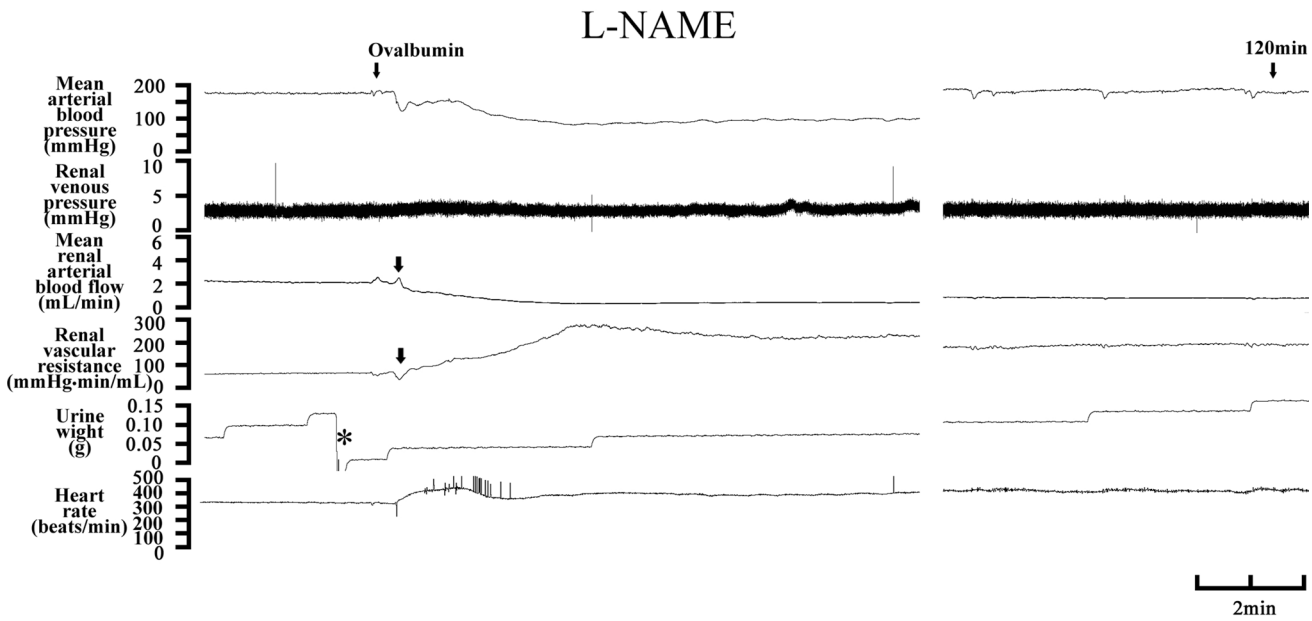

Fig. 2 Representative recordings of the responses of the variables to ovalbumin antigen (0.6 mg) in an anesthetized rat of the L-NAME anaphylaxis group. The *asterisk* indicates the artifact caused by the change of the urine collecting bottle. The *arrows* indicate a transient decrease in renal vascular resistance and an increase in renal arterial blood flow

After L-NAME pretreatment, MBP increased and RBF decreased: the baseline MBP and RBF in the L-NAME pretreated rats were significantly greater and smaller, respectively, than those in the D-NAME pretreated rats (Fig. 3). In the L-NAME anaphylaxis group, three rats died within 80 min after antigen presumably due to pulmonary edema as evidence by the presence of edema fluids in the trachea, while the antigen-induced decrease in MBP to the nadir of 70 mmHg at 5 min after antigen was smaller than that in the D-NAME group. In contrast to the D-NAME anaphylaxis group, RBF showed an initial increase by 9 ± 4% in three of seven rats studied. Of note, this increase in RBF occurred in accordance with the start of MBP fall, as shown in Fig. 2. Thereafter, RBF deceased to a nadir of 0.4 ± 0.1 ml/min, which was similar to the D-NAME anaphylaxis group at 6 min. However, RBF did not return to the baseline level but to the level which was almost half of that of D-NAME anaphylaxis group at the end of the experiment (Fig. 3b). Consequently, RVR at 6–8 min in the L-NAME anaphylaxis group increased twofold greater than that in the D-NAME anaphylaxis group and it remained significantly elevated until 80 min after antigen, as shown in Fig. 3c. Any parameters studied did not change significantly throughout the experimental period in the L-NAME control group (Fig. 3).

Urine flow in both D-NAME and L-NAME anaphylaxis groups changed similarly after antigen injection: it stopped and did not resume until 42 ± 4 and 60 ± 8 min after antigen. Thereafter, urine flow returned toward the baseline levels at 120 min after antigen in both anaphylaxis groups (Fig. 4a). No significant changes in urine flow were found in the control groups.

Figure 4b shows the results of creatinine clearance. Creatinine clearance at baseline in the L-NAME-pretreated rats tended to be greater than that in the D-NAME-pretreated rats. After antigen injection, creatinine clearance significantly decreased in both D-NAME and L-NAME anaphylaxis groups, while the post-antigen values in the L-NAME anaphylaxis group (32 ± 1% of baseline) were significantly smaller than those in the D-NAME anaphylaxis group (53 ± 3% of baseline) (Fig. 4c). In contrast, at 120 min of the end of the experiment, plasma creatinine levels in the D-NAME anaphylaxis group were not different from the baseline, whereas those in the L-NAME anaphylaxis group were significantly 1.7-fold higher than the baseline (Fig. 4d).

Isolated perfused kidney experiment

Figure 5a, b show representation examples of the responses of the D-NAME and L-NAME pretreated isolated rat kidneys, respectively. In Table 1, the changes are shown in the basal variables after treatment with L-NAME and D-NAME. Figure 6 shows the results of RBP, Q, and RVR after the antigen injection. In the D-NAME anaphylaxis group, the antigen caused renal vasoconstriction: RBP increased from the baseline value of 83 ± 2 mmHg to a peak of 147 ± 8 mmHg at 3.2 ± 0.3 min after antigen

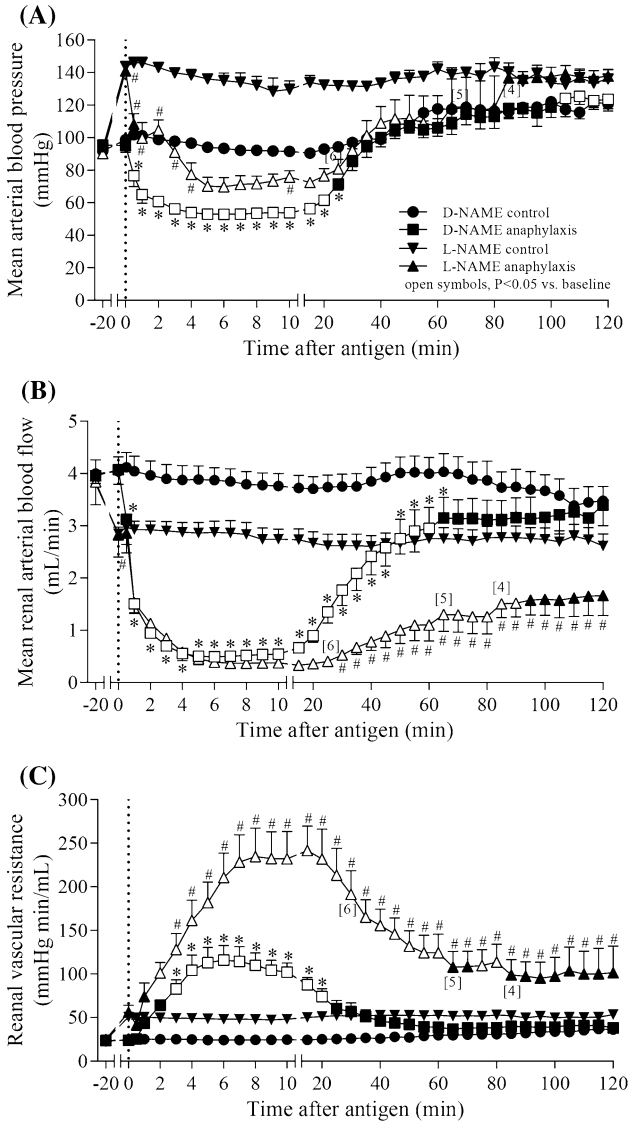

Fig. 3 Summary of changes in mean arterial blood pressure (**a**), mean renal arterial blood flow (**b**), and renal vascular resistance (**c**) in anesthetized rats. Mean ± SEM ($n = 7$); *circle*, the D-NAME control group; *square*, the D-NAME anaphylaxis group; *inverted triangle*, the L-NAME control group; *triangle*, the L-NAME anaphylaxis group; *open symbols*, $P < 0.05$ vs. baseline; $^{*}P < 0.05$ vs. the D-NAME control group; $^{\#}P < 0.05$ vs. the D-NAME anaphylaxis group. The *numbers in the parenthesis* for the L-NAME anaphylaxis group indicate the numbers of animals studied

(Fig. 6a). Consequently, RVR increased 1.7-fold from the baseline of 9.8 ± 0.3 mmHg min/ml/g to the peak of 17.5 ± 1.0 mmHg min/ml/g.

The administration of L-NAME caused an increase in RBP around 10 min. Thus we reduced Q by about 4 ml/min/g (Fig. 6b, Table 1) to obtain the stable baseline RBP, which was similar to that of D-NAME pretreated kidneys (Fig. 6a, Table 1). Pretreatment with L-NAME augmented the antigen-induced vasoconstriction, as reflected by a higher peak RBP of 238 ± 15 mmHg than that observed following D-NAME pretreatment (Fig. 6a). Consequently, the peak RVR after antigen in the L-NAME anaphylaxis group, 61.8 ± 3.8 mmHg min/ml/g, was significantly greater than that in the D-NAME anaphylaxis group (Fig. 6c).

Discussion

We determined the roles of NO in renal hemodynamic responses to the antigen in anesthetized and ovalbumin-sensitized rats and perfused kidneys isolated from the sensitized rats. After antigen injection, renal vasoconstriction occurred in sensitized rats as well as in isolated kidneys. L-NAME, an NO synthesis inhibitor, enhanced anaphylactic renal vasoconstriction in both anesthetized rats and isolated perfused rat kidneys. In anesthetized rats, renal dysfunction, as evidenced by a decrease in GFR, occurred within 120 min after antigen, and was deteriorated by L-NAME.

We for the first time determined renal hemodynamics during anaphylactic hypotension in anesthetized rats by measuring continuously RBF. Generally, it is believed that vasodilatation develops during anaphylaxis, but we have reported that it occurs only transiently and immediately after an injection of antigen, as reflected by a rapid and transient decrease in the total peripheral resistance, in anesthetized rats [24]. Actually, the blood flow of the mesenteric artery [2], hepatic artery [3], femoral artery [4], and gastric artery [5] transiently increased, followed by a rapid fall. The transient increase in blood flow may reflect a transient decrease in systemic vascular resistance (SVR) to 78% of the baseline at 1 min after antigen injection [24]. However, in the present study, we found slight and transient renal vasodilatation only in the presence of L-NAME, but not D-NAME. It is unknown why transient vasodilatation as observed in the above-mentioned arteries was not necessarily seen in the renal artery. On the other hand, it should be noted that vasodilatation occurred in the renal artery pretreated with L-NAME in the present study. This finding suggests no involvement of NO in transient vasodilatation at the early stage of anaphylaxis.

We showed that anaphylaxis caused renal vasoconstriction, resulting in reduction of RBF by 80% of baseline in anesthetized rats (Fig. 3b). Of note, this anaphylactic renal vasoconstriction was similar to that observed in splanchnic organs: the blood flow of the mesenteric artery [2], hepatic artery [3], and gastric artery [5] decreased by 75, 70, and 77%, respectively, of the pre-antigen level, when cardiac output decreased by 60% of the pre-antigen levels during anaphylactic hypotension [24]. In contrast, the blood flow of the femoral artery decreased only by 63.9%, which was comparable to the decreased cardiac output. However, renal vasoconstriction was stronger than that of the femoral artery

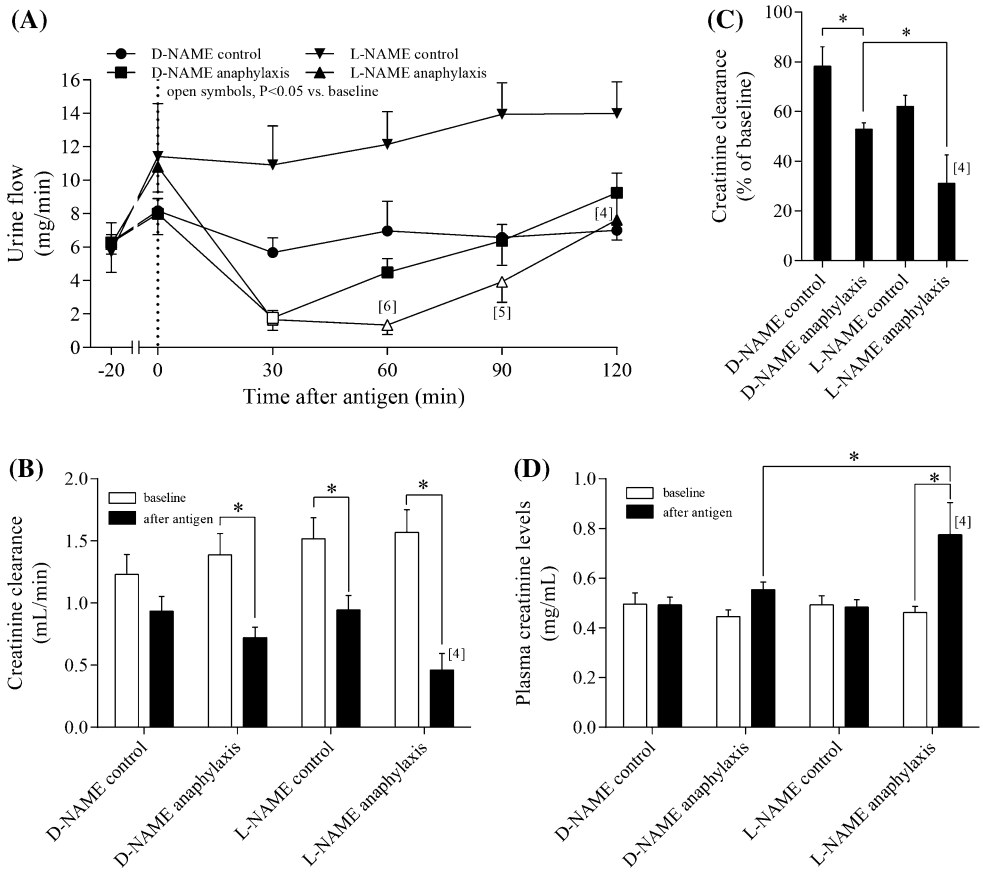

Fig. 4 Summary of the changes in urine flow (**a**), creatinine clearance (**b**, **c**) and plasma creatinine levels (**d**) in anesthetized rats. Mean ± SEM ($n = 7$); **a** *circle*, the D-NAME control group; *square*, the D-NAME anaphylaxis group; *inverted triangle*, the L-NAME control group; *triangle*, the L-NAME anaphylaxis group; *open symbols*, $P < 0.05$ vs. baseline; **b**, **d** *white and black bars* indicate the baseline values and the values at 120 min after antigen; **b**–**d** $*P < 0.05$. The *numbers in the parenthesis* for the L-NAME anaphylaxis group indicate that of animals or samples studied

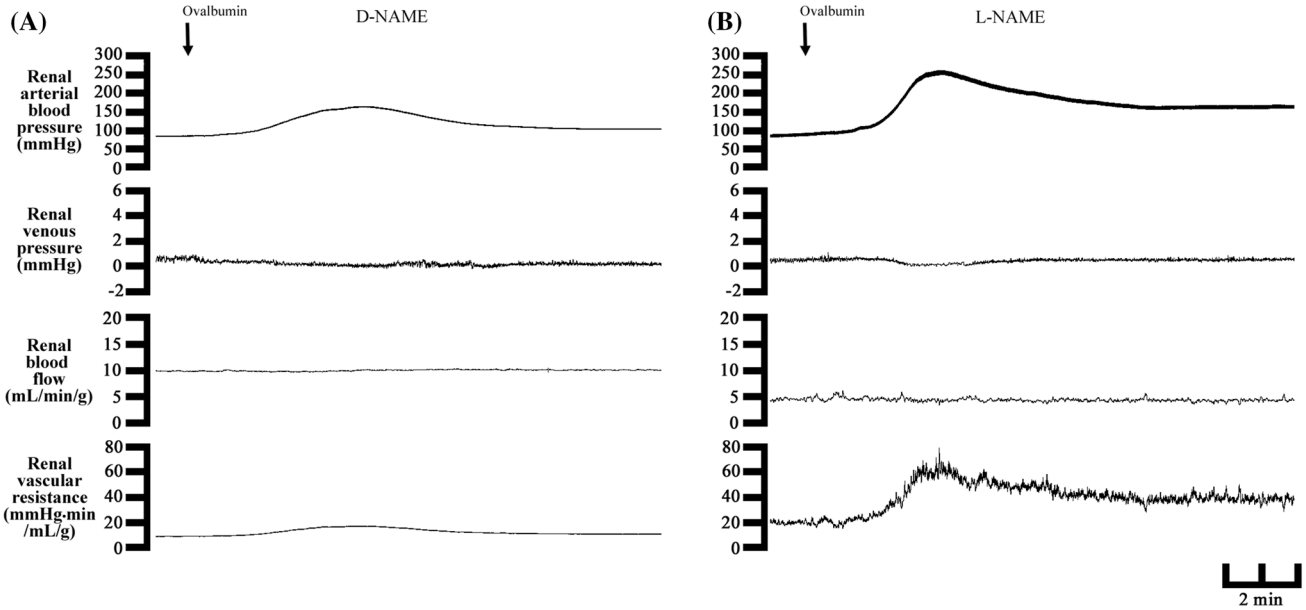

Fig. 5 Representative recordings of the responses of a perfused rat kidney to ovalbumin antigen (2 mg) in the D-NAME anaphylaxis group (**a**) and the L-NAME anaphylaxis group (**b**)

Table 1 The basal levels of the variables before and after administration of L-NAME or D-NAME in isolated perfused rat kidneys

Groups	L-NAME anaphylaxis ($n = 6$)		L-NAME control ($n = 6$)		D-NAME anaphylaxis ($n = 6$)		D-NAME control ($n = 6$)	
	Before	After	Before	After	Before	After	Before	After
Renal arterial blood pressure (mmHg)	73 ± 2	70 ± 7	65 ± 4	62 ± 7	78 ± 2	83 ± 2	86 ± 3	88 ± 5
Renal venous pressure (mmHg)	0.2 ± 0.1	0.1 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.2	0.8 ± 0.2
Mean renal arterial blood flow (ml/min/g)	6.7 ± 0.3	3.9 ± 0.2*†	7.4 ± 0.4	4.6 ± 0.7*†	8.5 ± 0.3	8.5 ± 0.3	8.0 ± 0.3	8.0 ± 0.3
Renal vascular resistance (mmHg min/ml/g)	11.1 ± 0.7	18.4 ± 2.2*†	8.8 ± 0.6	15.7 ± 3.7*	9.1 ± 0.4	9.8 ± 0.3	10.8 ± 0.9	11.1 ± 1.1

Values are mean ± SEM

* $P < 0.05$ vs. before

† $P < 0.05$, the D-NAME group vs. the L-NAME group

and similar to that in the splanchnic organs. Consistent with the present results, marked reduction of the blood flow to the kidney, as well as gastrointestinal tract, was observed in canine anaphylactic hypotension [25]. The presence of renal vasoconstriction contrasted to the absence of significant changes in SVR except the early stage of anaphylaxis, when SVR transiently decreased [24]. This renal vasoconstriction as well as vasoconstriction of splanchnic organs [2, 5] may function to compensate for the fall in MBP and counteract the anaphylaxis-induced vasodilatation, resulting in no significant changes in SVR during systemic anaphylaxis in anesthetized rats [24].

The antigen-induced renal vasoconstriction is ascribed mainly to direct vasoconstrictive actions of anaphylactic mediators, because it is observed in isolated perfused kidneys, independently of humoral and neural factors. Actually, it is reported that histamine [26], leukotrienes [26, 27], thromboxane (Tx) A_2 [26, 28], serotonin [29], and PAF [30] constrict renal artery. Another possibility is related to activation of renal sympathetic nerve activity, which could result in renal vasoconstriction [31]. Actually, it is reported that the renal sympathetic activity increases during anaphylactic hypotension in anesthetized rats [32, 33]. Finally, humoral factors such as angiotensin II and vasopressin, which are released during anaphylactic hypotension of anesthetized rats [34] could constrict renal vessels [35, 36].

Our results showed that L-NAME enhanced anaphylactic renal vasoconstriction in both the isolated perfused rat kidneys and anesthetized rats. These findings are consistent with those of previous studies showing the release of endogenous NO during anaphylaxis in the isolated pulmonary artery [11, 12] and mesenteric artery [14], coronary arteries of the isolated heart [15, 16], or veins of the isolated liver [17, 18]. These findings suggest that NO is produced during systemic anaphylaxis and then attenuates anaphylactic constriction of the vessels. It is reported that NO, which is produced by endothelial NO synthase in anaphylactic hypotension, plays a role in hypotension [9].

The mechanism for anaphylaxis-induced NO production could be explained by two ways: Anaphylactic mediators such as histamine [37], PAF [38], TxA_2 [37], and leukotrienes [39], are reported to induce NO release from the vascular endothelial cells in response to anaphylaxis. Another possibility seems to be related to shear stress: Anaphylaxis constricts renal vessels, where shear stress is invariably increased, resulting in NO release from the endothelium. Actually renal vasoconstriction induced by angiotensin II [36] and vasopressin [35] is accompanied by NO production, as reflected by augmented vasoconstriction by L-NAME.

We measured GFR by assessing creatinine clearance in anesthetized rats. Of note, baseline GFR in the L-NAME groups tended to be greater, but not significantly, than that in the D-NAME groups. The finding that GFR showed a small, statistically insignificant increase after L-NAME is in accordance with the previous reports [20, 40]. The L-NAME-induced increase in GFR may be ascribed to predominant constriction of rat post-glomerular vessels [20–22], resulting in elevation of the filtration pressure, the primary determinant of GFR, which might overcome the L-NAME-induced reduction of glomerular blood flow, another determinant of GFR. In the present study, we found that anaphylaxis caused a decrease in GFR and that L-NAME augmented this anaphylaxis-induced GFR reduction. The pathogenesis of decreased GFR is not known in the present study. We assume that anaphylaxis-induced decrease in RBF accounts for GFR reduction, since the magnitudes of decreased GFR seem to be similar to those of RBF, as shown in Figs. 3b, 4b, c. Actually, RBF of the L-NAME anaphylaxis group at 120 min was nearly 50% that of the D-NAME anaphylaxis group (Fig. 3b), while GFR of the former group was half of that of the latter group (Fig. 4b). We think that anaphylactic mediators might have not damaged the glomerular capillaries so much. Further study is required in this respect.

In summary, the renal vascular response to the antigen is vasoconstriction, which is enhanced by L-NAME in both isolated perfused rat kidneys and anesthetized rats, and is accompanied by a reduction of GFR, which is also

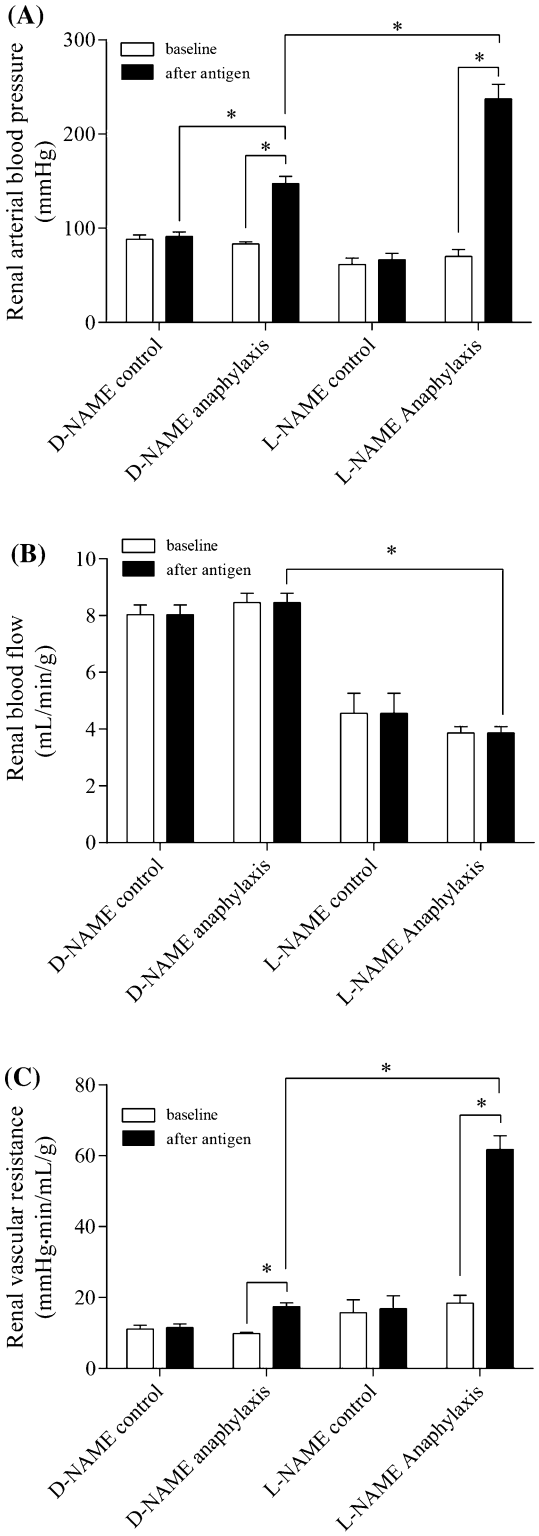

Fig. 6 Summary of the renal arterial pressure (**a**), renal blood flow (**b**), and renal vascular resistance (**c**). Mean ± SEM ($n = 6$); *white bars*, the baseline; *black bars*, the values at the peak of renal vasoconstriction; $^*P < 0.05$

augmented by L-NAME. These results suggest that renal anaphylaxis causes renal vasoconstriction, which is inherently attenuated by NO generated in the kidneys.

Author contributions KM, YuK, and TS contributed to study design, data acquisition, data analysis, data interpretation and manuscript writing. MT contributed to data acquisition and data interpretation. YaK and HY contributed to data interpretation and manuscript writing. All authors approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Statement on the welfare of animals All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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