Effect of L-$N^G$-Nitro-Arginine, Inhibitor of Nitric Oxide Synthesis, on Autoregulation of Renal Blood Flow in Dogs

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ABSTRACT—The present experiments were designed to evaluate the importance of nitric oxide in the regulation of renal hemodynamics and the autoregulation of renal blood flow (RBF) in anesthetized dogs. RBF was measured by an electromagnetic flowmeter, and renal arterial pressure (RAP) was varied by an adjustable aortic clamp. The RAP-RBF relations were examined during the intrarenal infusion of saline or agents. The intrarenal infusion of L-$N^G$-nitro-arginine (L-NNA, 40 μg/kg·min) at normal RAP decreased RBF and urine flow (UF), while the infusion of L-arginine·HCl (1 mg/kg·min) increased RBF and UF. Both agents did not affect the glomerular filtration rate and mean arterial pressure. The autoregulation of RBF was impaired during the L-NNA infusion. The L-arginine infusion did not affect autoregulatory efficiency. When L-NNA (40 μg/kg·min) and L-arginine were infused simultaneously into the renal artery, the autoregulation of RBF was maintained. However, a higher dose of L-NNA (200 μg/kg·min) impaired the autoregulation of RBF. These results suggest that the basal production and/or the release of nitric oxide contributes to the regulation of renal hemodynamics and urine formation. During the reduction of RAP, nitric oxide may play an important role in the autoregulation of RBF.

The kidney can maintain its blood flow over a wide range of pressures. However, there is still no consensus about the possible mechanisms involved in this autoregulatory behavior. At present, controversy centers around the importance of the myogenic hypothesis and the tubulo-glomerular feedback hypothesis (1–3). In our previous study, which was designed to clarify the relative importance of the above two hypotheses in in vivo experiments using the whole kidney, the autoregulation of renal blood flow (RBF) was observed in a nonfiltering kidney, in which the tubulo-glomerular feedback system may have been impaired (3). Thus, we believe that the myogenic hypothesis is relatively important.

In 1980, Furchgott and Zawadzki (4) demonstrated that acetylcholine induced vascular relaxation was dependent on the presence of a functionally intact endothelium. They also postulated that a labile humoral factor, termed endothelium-derived relaxing factor (EDRF), was released from endothelial cells. More recently, Palmer et al. (5, 6) and Ignarro et al. (7) have provided evidence that EDRF activity is due to the release of nitric oxide (NO), which originates from the terminal guanidino nitrogen atom of the amino acid L-arginine.
Since then, there have been many reports concerning the role of EDRF/NO in the regulation of systemic or organ circulation. The intravenous infusion of $L-N^2$-monomethyl-arginine, one of the nitric oxide synthesis inhibitors, increased systemic blood pressure in experimental animals (8–10). Conversely, $L$-arginine decreased systemic blood pressure in humans (11). Thus, it can be considered that EDRF/NO plays an important role in the modulation of vascular tone. Rubanyi (12) reported that a pressure-induced contraction of an isolated canine carotid artery was endothelium-dependent and that increases in pressure depressed the synthesis and/or release of EDRFs. These findings may indicate that EDRF/NO plays a crucial role in the autoregulation of RBF.

The present experiment was therefore designed to evaluate the importance of nitric oxide in the regulation of renal hemodynamics and the autoregulation of RBF. The pressure-flow relations were examined before and during the intrarenal infusions of $L-N^2$-nitro-arginine ($L$-NNA), one of the EDRF/NO synthesis inhibitors, and $L$-arginine into pentobarbital anesthetized dogs.

MATERIALS AND METHODS

All experiments were performed on adult male mongrel dogs, weighing 10–24 kg, that had been maintained on a standard laboratory diet for 1 week. All dogs were deprived of food 24 hr before the experiments. The dogs were anesthetized with pentobarbital sodium (30 mg/kg, i.v.), followed by a maintenance dose when necessary. Following tracheal intubation, each dog was ventilated mechanically with room air. Polyethylene catheters were placed in the right brachial artery and vein for arterial blood sampling and monitoring of systemic arterial pressure and for the infusion of saline and inulin, respectively. Another catheter was also placed in the abdominal aorta just below the bifurcation of the left renal artery via the right femoral artery, and renal arterial pressure (RAP) was continuously monitored with a pressure transducer and recorded on a polygraph (model No. 361, NEC San-eci, Japan).

The left kidney was exposed through a retroperitoneal flank incision. The kidney was then carefully denervated by dissecting all visible nerve fibers and the tissue connecting the renal hilum cephalad to the renal artery. RBF was measured by an electromagnetic flow-meter (MFV-1200, Nihon Kohden, Japan). A stainless steel adjustable clamp was placed on the aorta just above the bifurcation of the left renal artery, which was used to vary RAP. A small curved 23-gauge needle was inserted into the left renal artery proximal to the flow probe for the intrarenal infusion of isotonic saline or agents. This was maintained patent by a continuous infusion of isotonic saline at the rate of 0.19 ml/min. Simultaneously, an intravenous infusion of isotonic saline at the rate of 2 ml/min was started. For the measurement of glomerular filtration rate (GFR), a priming dose of inulin (100 mg/kg) was given into the right brachial vein, followed by a continuous infusion at a rate of 100 mg/kg per hour to maintain a constant blood level of inulin. A polyethylene catheter was inserted into the left ureter for urine collection. After completion of surgery, the dog was left for 60–90 min to allow for the stabilization of systemic blood pressure and RBF. Four series of experiments were performed as follows:

1) Effects of $L$-NNA on renal function and autoregulation of RBF: After stabilization of mean arterial pressure (MAP), RBF and urine flow (UF), urine was collected during two consecutive 10-min control clearance periods. At the midpoint of each period, a sample of systemic arterial blood was collected. Following tracheal intubation, each dog was ventilated mechanically with room air. Polyethylene catheters were placed in the right brachial artery and vein for arterial blood sampling and monitoring of systemic arterial pressure and for the infusion of saline and inulin, respectively. Another catheter was also placed in the abdominal aorta just below the bifurcation of the left renal artery via the right femoral artery, and renal arterial pressure (RAP) was continuously monitored with a pressure transducer and recorded on a polygraph (model No. 361, NEC San-eci, Japan).

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1) Effects of $L$-NNA on renal function and autoregulation of RBF: After stabilization of mean arterial pressure (MAP), RBF and urine flow (UF), urine was collected during two consecutive 10-min control clearance periods. At the midpoint of each period, a sample of systemic arterial blood was collected. After a 2nd control clearance period, an intrarenal infusion of $L$-NNA was started at the rate of 40 $\mu$g/kg-min in 5 dogs. A urine sample was collected between 25 min and 35 min, and a blood sample was obtained at 30 min after the start of $L$-NNA infusion. In another 8 dogs, the pressure-flow relations were obtained during an intrarenal infusion of isotonic saline. RAP was sequentially altered in 5 steps as in-
icated in Fig. 1: basal pressure, 100, 75, 50 and 25 mmHg. A reduction of RAP within the autoregulatory pressure range resulted in a transient reduction of RBF, lasting 10–20 sec, which recovered to the control level of RBF within 1 min. Therefore, each pressure level was maintained for a few minutes to allow a complete autoregulatory response. RAP was then returned to the control level after a trial of pressure reduction. The animals were then left for 30 min to allow for stabilization of RBF. An intrarenal infusion of L-NNA was started at the rate of 40 μg/kg·min. Thirty minutes after the start of L-NNA infusion, the pressure-flow relations were examined as described above. In an additional 4 dogs, the pressure-flow relations were examined twice, at 60-min interval to test the reproducibility of this relation.

2) Effects of L-arginine on renal function: After a 2nd control clearance period, L-arginine·HCl was infused into the renal artery at the rate of 1 mg/kg·min in 5 dogs. Urine and blood samples were taken during L-arginine infusion in the same way as described for L-NNA.

3) Combined effects of L-NNA and L-arginine on renal function and autoregulation of RBF: L-arginine alone was infused into the renal artery at the rate of 1 mg/kg·min after a 2nd control clearance period. A urine sample was collected between 25 min and 35 min, and a blood sample was obtained at 30 min after the start of L-arginine infusion. Following this clearance study, L-NNA (40 μg/kg·min) was superimposed on the L-arginine infusion in 5 dogs. Urine and blood samples were obtained between 25 min and 35 min, and at 30 min after the start of combined infusion. In another 6 dogs, the pressure-flow relations were obtained at 30 min after the start of the intrarenal infusion of L-arginine (1 mg/kg·min). After releasing the aortic clamp, the dogs were left for 30 min. L-NNA (40 μg/kg·min) was then superimposed on the L-arginine infusion. At 30 min after the treatment of L-arginine and L-NNA, the pressure-flow relations were again obtained. In an additional 4 dogs, a higher dose of L-NNA (200 μg/kg·min) was superimposed on the L-arginine, and pressure-flow relations were obtained in the same way as described above.

4) Effects of d-NG-nitro-arginine and D-arginine on renal hemodynamics: In 3 dogs, an intrarenal infusion of d-NG-nitro-arginine (d-NNA) at the rate of 40 μg/kg·min was performed. In an additional 4 dogs, an intrarenal infusion of D-arginine at the rate of 1 mg/kg·min was performed. During these experiments, renal hemodynamic actions were examined in all the dogs.

Plasma and urine concentration of inulin was determined by the method of Walser et al. (13). The urine concentration of sodium was measured with a flame photometer (Hitachi 750, Japan). L-NNA, d-NNA, L-arginine and D-arginine were purchased from Peptide Institute, Inc. (Osaka, Japan) and were dissolved in isotonic saline. The present data are expressed as means ± S.E. Statistical analysis within groups were performed using the paired t-test, and P values less than 0.05 were regarded as significant.

RESULTS

Effects of L-NNA and L-arginine on renal function and hemodynamics at normal renal arterial pressure

Table 1 shows the effects of L-NNA and L-arginine on MAP, RBF, GFR, UF and urinary excretion of sodium (UNaV). The intrarenal infusion of L-NNA at the rate of 40 μg/kg·min resulted in significant decreases of RBF and UF with no change in MAP. UF decreased but UNaV did not change during L-NNA infusion. In contrast to L-NNA, the intrarenal infusion of L-arginine at a rate of 1 mg/kg·min caused significant increases of RBF and UF with no change in MAP. Both agents did not affect GFR. The superimposition of L-NNA to the L-arginine infusion cancelled out the effects caused by the L-arginine infusion, and all parameters reverted to the control level (Table 2). L-NNA and L-arginine seemed to have contrary effects on RBF and
urine flow to each other. The intrarenal infusion of D-NNA at the rate of 40 \( \mu \text{g/kg-min} \) and D-arginine at the rate of 1 mg/kg-min did not affect any parameters of renal function and hemodynamics (data not shown).

**Table 1. Effects of L-NG-nitro-arginine and L-arginine on renal hemodynamics and urine formation in anesthetized dogs**

|                      | MAP (mmHg) | RBF (ml/g-min) | GFR (ml/g-min) | UF (\( \mu \text{l/g-min} \)) | \( \text{U}_{\text{Na}} \text{V} \) (\( \mu \text{Eq/g-min} \)) |
|----------------------|------------|----------------|----------------|---------------------|-------------------------|
| Control              | 120 ± 7    | 3.11 ± 0.35    | 0.94 ± 0.09    | 6.8 ± 1.5           | 0.69 ± 0.25             |
| L-NG-nitro-arginine (40 \( \mu \text{g/kg-min} \)) | 122 ± 7    | 2.62 ± 0.43*   | 0.96 ± 0.10    | 4.4 ± 0.5*           | 0.73 ± 0.32             |
| 30 min               | 123 ± 4    | 3.13 ± 0.28    | 0.84 ± 0.03    | 4.2 ± 0.5           | 0.66 ± 0.15             |
| L-arginine-HCl (1 mg/kg-min) | 124 ± 4    | 3.39 ± 0.29*   | 0.82 ± 0.03    | 5.4 ± 0.8*          | 0.74 ± 0.20             |

All values are means ± S.E. (\( n = 5 \)). In each group, the control values were obtained during the 2nd control clearance period. * indicates a significant difference from each control value (\( P < 0.05 \)). Abbreviations: MAP = mean arterial pressure, RBF = renal blood flow, GFR = glomerular filtration rate, UF = urine flow, \( \text{U}_{\text{Na}} \text{V} \) = urinary sodium excretion.

**Table 2. Effects of L-arginine and L-NG-nitro-arginine in combination on renal hemodynamics and urine formation in dogs**

|                      | MAP (mmHg) | RBF (ml/g-min) | GFR (ml/g-min) | UF (\( \mu \text{l/g-min} \)) | \( \text{U}_{\text{Na}} \text{V} \) (\( \mu \text{Eq/g-min} \)) |
|----------------------|------------|----------------|----------------|---------------------|-------------------------|
| Control              | 125 ± 7    | 2.88 ± 0.28    | 0.84 ± 0.06    | 8.0 ± 2.4           | 1.3 ± 0.5               |
| L-arginine-HCl (1 mg/kg-min) | 128 ± 8    | 3.11 ± 0.27*   | 0.82 ± 0.06    | 11.2 ± 2.8*         | 1.8 ± 0.4*              |
| 30 min               | 129 ± 7    | 2.91 ± 0.29    | 0.85 ± 0.07    | 8.4 ± 2.2           | 1.3 ± 0.4               |

All values are means ± S.E. (\( n = 5 \)). The control values were obtained during the 2nd control clearance period. * indicates a significant difference from each control value (\( P < 0.05 \)). Abbreviations: MAP = mean arterial pressure, RBF = renal blood flow, GFR = glomerular filtration rate, UF = urine flow, \( \text{U}_{\text{Na}} \text{V} \) = urinary sodium excretion.

urine flow to each other. The intrarenal infusion of D-NNA at the rate of 40 \( \mu \text{g/kg-min} \) and D-arginine at the rate of 1 mg/kg-min did not affect any parameters of renal function and hemodynamics (data not shown).

**Effect of L-NNA on autoregulation of RBF**

Figure 1B shows the relationship between RAP and RBF in the absence (saline control) and the presence of L-NNA. When RAP was reduced from the basal pressure to 75 mmHg, RBF remained constant in the saline control group. The RBF at the basal pressure and 75 mmHg were 3.16 ± 0.14 and 3.23 ± 0.15 ml/g-min, respectively. There was no significant difference between these values. The intrarenal infusion of L-NNA (40 \( \mu \text{g/kg-min} \)) resulted in a significant decrease of RBF. Thirty minutes after the start of the L-NNA infusion, autoregulatory capability of RBF was impaired as shown in Fig. 1B. That is, RBF decreased pressure-dependently. To more strictly evaluate autoregulation, the efficiency of autoregulation of RBF was analyzed by a paired comparison of the autoregulation factors between the saline control and agents in-
fusion, using identical pressure steps in the same dogs. The autoregulation factor was calculated using the formula of Semple and De Wardener (14).

\[
\text{autoregulation factor} = \frac{RBF_2 - RBF_1}{RBF_1} \div \frac{\text{RAP}_2 - \text{RAP}_1}{\text{RAP}_1}
\]

The value is inversely related to autoregulatory efficiency: a value of 1 indicates no autoregulation, whereas values near 0 indicate a high efficiency of autoregulation.

In the saline control, the autoregulation factors of step I (basal pressure = 100 mmHg) and step II (100–75 mmHg) were near 0, thereby indicating a complete autoregulation of RBF. During the intrarenal infusion of L-NNA, the autoregulation factors of steps I and II were significantly higher than those in the saline control (Fig. 1B). Thus, autoregulation was impaired by the infusion of L-NNA.

Fig. 1. The reproducibility of the autoregulation of renal blood flow (RBF, panel A) and effect of L-N^G^-nitro-arginine (L-NNA) on autoregulation of RBF (panel B). In the upper panel of A, the solid (---) and broken (---●--) lines indicate the relationships between the renal arterial pressure (RAP) and RBF at the 1st and 2nd trials of pressure reduction, respectively (n = 4). The lower panel of A shows the calculated autoregulation factors at each step. Steps I, II and III express each trial of pressure reduction (step I = basal pressure – 100 mmHg, step II = 100–75 mmHg, step III = 75–50 mmHg). The open (□) and solid (■) bars indicate the 1st and 2nd trials of pressure reduction, respectively. In the upper panel of B, the solid (---) and broken (---●--) lines indicate RAP-RBF relations before and during the infusion of L-NNA at the rate of 40 μg/kg/min, respectively (n = 8). In the lower panel of B, the open (□) and hatched (■) bars indicate the control and L-NNA infusion, respectively. An asterisk indicates a significant difference from each control value (P < 0.05).
The reproducibility of the pressure-flow relation was examined in the same animal, twice, at 60-min interval. Figure 1A clearly indicates the complete reproducibility of the autoregulation of RBF in anesthetized dog kidney.

**Combined effect of L-NNA and L-arginine on autoregulation of RBF**

The L-arginine infusion (1 mg/kg-min) increased RBF, and the autoregulation of RBF was maintained during the L-arginine infusion (Fig. 2). The superimposition of L-NNA (40 μg/kg-min) on the L-arginine infusion for 30 min decreased RBF slightly, but did not affect the autoregulatory efficacy of RBF. Calculated autoregulation factors of steps I and II in L-arginine and the combined infusion of L-NNA and L-arginine were kept near 0, indicating the complete autoregulation of RBF (Fig. 2A). However, when a higher dose of L-NNA (200 μg/kg-min) was superimposed to the L-arginine infusion for 30 min, RBF decreased to the level of L-NNA (40 μg/kg-min) alone, and the autoregulation of RBF was significantly impaired (Fig. 2B).

**Fig. 2.** The combined effects of L-arginine and L-NNA (lower dosage: panel A, higher dosage: panel B) on the autoregulation of renal blood flow (RBF). The upper panel of A expresses the renal arterial pressure (RAP)-RBF relations during the infusion of L-arginine (solid line, -○-) at the rate of 1 mg/kg-min and the superimposition of L-NNA (broken line, •••••••) at the rate of 40 μg/kg-min, respectively (n = 6). The upper panel of B expresses RAP-RBF relations during the infusion of L-arginine (solid line, -○-) at the rate of 1 mg/kg-min and the superimposition of L-NNA (broken line, •••••••) at the rate of 200 μg/kg-min, respectively (n = 4). The lower panels of A and B indicate the calculated autoregulation factors at each step as described in the legend of Fig. 1. The open bars (□) indicate the L-arginine results. The hatched bars (panel A, □□) and the solid bars (panel B, ■) show the results of the superimposition of L-NNA (40 and 200 μg/kg-min, respectively) onto L-arginine. An asterisk indicates a significant difference from each L-arginine result (P < 0.05).
DISCUSSION

In the present in vivo experiments, an intrarenal infusion of L-NNA, an inhibitor of EDRF/NO synthesis, caused a decrease in RBF and UF at normal RAP, but D-NNA did not. On the contrary, L-arginine increased RBF and UF, but D-arginine did not. These findings indicate that nitric oxide may be synthesized and released in the basal condition in the kidney and that this basal release of nitric oxide contributes to the regulation of renal hemodynamics and urine formation. However, based on the present results, we could not exactly define the antidiuretic mechanism of L-NNA since the L-NNA infusion decreased urine flow, but did not affect UNaV.

Since Furchgott and Zawadzki (4) proposed the function of EDRF in 1980, evidence that EDRF plays a role in the regulation of renal vascular tone have accumulated. However, these evidence were obtained mostly from in vitro studies. Using the isolated perfused kidney of the rat, Radermacher et al. (15) reported that L-NNA and gossypol, an inhibitor of EDRF production and/or release, increased basal renal vascular resistance. Bhardwaj and Moore (16) reported that L-arginine, itself, plays as a vasodilator in the perfused rat kidney. Thus, the present in vivo results confirm these previous reports, indicating basal production of EDRF/NO in the kidney. However, there have been many reports that nitric oxide can be synthesized in various tissues besides endothelial cells, e.g., vascular smooth muscle (17), nervous system (18, 19), etc. In addition, endothelium was not denuded in the present experiments since the application of various endothelium-toxic compounds resulted in endothelial disruption. This was followed by a rapid deterioration of organ blood flow and the development of edema and microthrombi (20). Therefore, we could not define whether the renal hemodynamic changes induced by L-NNA and L-arginine were produced via the nitric oxide synthesized in the endothelium or that synthesized in other renal tissues.

Renal autoregulation is a well-established phenomenon, in which the RBF is maintained relatively constant, over a wide range of RAP through changes in resistance vessels (21–24). Since Bayliss (25) demonstrated in 1902 that vascular smooth muscle responds to the changes of transmural pressure, it has been believed that the changes of transmural pressure and wall tension could trigger the autoregulation of RBF. A reduction in RAP may trigger smooth muscle dilation by modifying the synthesis and/or release of vasoactive substances in the kidney. The participation of the renin-angiotensin system and prostanoids, as vasoactive substances, can be ruled out by our experiments and those of others, which show that the autoregulation can be maintained in the presence of an angiotensin II receptor antagonist or indomethacin (23, 26). Therefore, EDRF/NO is an attractive candidate for the vasoactive substance that triggers the autoregulation of RBF. Recently, Rubanyi (12) and Harder (27) reported that the myogenic response to the change of transmural pressure was endothelium-dependent. In the present in vivo experiments, we have demonstrated that L-NNA abolished the autoregulatory behavior. Conversely, L-arginine increased RBF by approximately 10% without any changes in systemic arterial pressure, indicating significant renal vasodilation. It has been reported that vasodilators such as acetylcholine and calcium antagonists impair the autoregulation of RBF (24, 28). However, the autoregulation of RBF was maintained fairly well during the L-arginine infusion, even though the renal vascular resistance was significantly reduced. Decreased RBF during the superimposition of L-NNA to the L-arginine infusion was dose-dependent. The 40 μg/kg-min-dosage of L-NNA with L-arginine did not impair the autoregulatory behavior, but a higher dose of L-NNA with L-arginine impaired it to the same extent as the lower dosage of L-NNA alone. These observations indicate that there may be a close relationship between RAP and nitric oxide synthesis. That is, the reduction of RAP may stimulate the release and/or synthesis of nitric
oxide in the renal tissue. As mentioned above, we could not define the exact site of nitric oxide synthesis in the kidney. However, as we have previously reported, the autoregulation of RBF exists even in a nonfiltering kidney without functional macula densa cells and tubular cells (3). In addition, the present experiments were performed using a denervated kidney. Taken together, these findings indicate that the site of nitric oxide synthesis may be the renal vasculature and/or endothelial cells.

Concerning the impairment of autoregulation by L-NNA, several factors besides the inhibition of nitric oxide synthesis should be considered. The first is the rise in renal vascular resistance induced by L-NNA infusion itself. An increase of the renal vascular resistance or a decrease of RBF itself is not a causal factor for the impairment of autoregulation, since the increase in renal vascular resistance induced by angiotensin II or noradrenaline did not affect autoregulatory behavior (29). The second factor is the reproducibility of the autoregulation of RBF. There is no difference between the two pressure-flow relations obtained at 60-min interval as shown in Fig. 1A. Thus, these evidence suggest that the inhibition of nitric oxide synthesis by L-NNA during the reduction of RAP impairs the autoregulation of RBF.

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