Role of Nitric Oxide and Angiotsensin II in Diabetes Mellitus-Induced Glomerular Hyperfiltration1,2

Karen M. Mathis and Robert O. Banks3

K.M. Mathis, R.O. Banks, Department of Molecular and Cellular Physiology, University of Cincinnati College of Medicine, Cincinnati, OH

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ABSTRACT

The goal of this study was to determine to what extent nitric oxide (NO) and/or angiotensin II (AngII) are involved in the hyperfiltration observed in rats with streptozotocin-induced diabetes mellitus. Studies were performed on anesthetized rats 7 to 10 days after the induction of diabetes. Nitro-L-arginine (LNA) was used to inhibit NO synthesis, and losartan was used to block AngII receptors. Three protocols were utilized: (i) control and diabetic rats treated with a constant infusion of LNA; (ii) control and diabetic rats treated first with a constant infusion of losartan and then LNA plus losartan; and (iii) nephrectomized control and diabetic rats treated with LNA (to evaluate the involvement of renal vasoactive factors other than AngII in the systemic response to LNA). Compared with controls, diabetics had a significantly elevated baseline GFR but the same mean arterial pressure (MAP). In Protocol i, LNA caused the same increase in MAP in both groups but only decreased the GFR in controls. In Protocol ii, losartan caused a significant increase in the GFR only in controls. The coinfusion of LNA and losartan caused no change in the GFR in controls but induced a large GFR decrease in diabetics. Losartan had no effect on MAP in either group and did not affect the LNA-induced increase in MAP in either group. The LNA-induced increase in MAP was greater in nephrectomized rats compared with that in intact rats. These data indicate that (1) neither changes in the synthesis of NO nor changes in the actions of AngII, alone, are responsible for the hyperfiltration observed in streptozotocin-induced diabetes; (2) a combined alteration in these two systems may account for diabetes-induced hyperfiltration; (3) the LNA-induced decrease in GFR in control but not in diabetic rats is an AngII-mediated event; and (4) AngII is not involved in the LNA-induced increase in MAP in either control or diabetic rats but other renal factors cannot be ruled out in this response.

Key Words: GFR, streptozotocin, nitro-L-arginine, losartan, rat

One of the characteristic hallmarks of both diabetic patients and streptozotocin-induced diabetic rats is an increased GFR during the early stages of the disease (1). This hyperfiltration is followed by structural changes that eventually lead to impaired renal function (2). A number of mechanisms have been advanced to account for this initial increase in GFR, including; increased filtration surface area (2), increased polyol pathway activity (3), increased growth hormone secretion (4), increased production of nitric oxide (NO) (5–7), and increased production of bradykinin (8). With regard to the NO system, several in vitro studies have concluded that diabetic animals have a decreased production and/or responsiveness to NO (9–12). However, measurements made in vivo indicate that there is actually an increase in endogenous NO production in diabetic rats (5–7).

Disturbances in the renin angiotensin system (RAS) have also been reported in diabetic rats. Hyperresponsiveness to angiotensin II (AngII) in combination with a decrease in PRA (13,14) has been documented. On the other hand, others have reported a decrease in AngII receptors with no change in angiotensinogen or renin mRNA levels (15). In addition, other investigators have shown that although intrarenal renin protein content and renin and angiotensinogen mRNA levels are increased in diabetic rats, renal angiotensin-converting enzyme (ACE) activity is significantly reduced (16).

The interaction between NO and the RAS has been studied in basal states in a number of in vivo preparations, often with conflicting results. It has been shown that the intrarenal basal release of NO may act as an inhibitory modulator of the release of renin in the whole animal (17). Furthermore, several authors have demonstrated in the anesthetized rat that the decrease in RBF (18,19) and GFR (19) but not the increase in blood pressure (18,19) in response to the inhibition of NO synthesis occurs because of AngII. However, in studies utilizing conscious rats, Baylis et al. (20) have demonstrated that the renal hemodynamic response to NO inhibition is not the result of AngII. By contrast, studies using the long-term inhibition of NO synthesis in conscious rats have demonstrated that the resulting hypertension is in fact AngII dependent (21,22).

The aim of this study was to determine the extent to which NO, the RAS, or a combination of the two
systems contributes to the hyperfiltration observed in diabetes mellitus. If the NO system is perturbed in diabetes mellitus, the inhibition of NO synthesis should normalize the hyperfiltration observed in diabetic rats. By the same token, antagonism of AngII should normalize the GFR in diabetic rats if disturbances in the RAS are responsible for the hyperfiltration. Concomitant alterations in both systems would be revealed by simultaneous NO inhibition and blockade of the RAS. The renal and systemic actions of an NO synthase inhibitor (23), nitro-l-arginine (LNA), and of an AngII receptor antagonist, losartan (24), which does not have agonist effects, were evaluated under steady-state conditions in pentobarbital-anesthetized female control and diabetic rats.

MATERIALS AND METHODS

Experiments were performed on a total of 40 female Sprague-Dawley rats (197 to 312 g); all studies were done in accordance with institutional guidelines and approved by the Institutional Animal Care and Use Committee. Animals were maintained on standard rat chow and water ad libitum until the time of the experiment. After a 24-h fast, diabetes mellitus was induced by an ip injection of 65 mg/kg streptozotocin (STZ). The onset of diabetes was defined as the day the urinary glucose concentration reached 1,000 mg/dL; urinary glucose was monitored with Diastix reagent strips. All experiments were conducted 7 to 10 days after the onset of diabetes. Blood glucose was measured on the day of the experiment with Glucostix reagent strips. On the day of the experiment, rats were anesthetized with sodium pentobarbital (65 mg/kg), and rectal temperatures were maintained at 37 ± 0.5°C with a radiant heat lamp connected to a temperature controller. The left femoral artery was cannulated with PE-50 tubing and used for monitoring mean arterial blood pressure (MAP) and collecting blood samples. The left femoral vein was cannulated with PE-50 tubing and used for the infusion of saline containing 3% creatinine and experimental solutions at 24 μL/min in order to match urine output of 30 ± 5 μL/min as closely as possible; because preliminary experiments with diabetic rats (N = 6) demonstrated that the urine flow rate during the stabilization period following surgery averaged 118 ± 13 μL/min, solutions were infused at 106 μL/min, again, in order to closely match the rate of urine output. The bladder was cannulated with PE-100 tubing for the collection of urine. After the completion of surgery, in order to facilitate the complete collection of urine, the animal was placed on its side above the level of the table. After surgery and a 60-min stabilization period, 3 × 20-min baseline clearances were collected; individual protocols are delineated below.

Protocol i: Effects of LNA on GFR and MAP in Control and Diabetic Rats

To determine to what extent diabetes-related glomerular hyperfiltration is caused by elevated NO synthesis, eight control and six diabetic rats were infused with the NO synthesis inhibitor LNA, i.e., if the elevated GFR in diabetic rats is caused by an increased NO synthesis, LNA should normalize the GFR between control and diabetic rats. After the collection of baseline clearances, LNA was infused at 50 μg/kg per min for 60 min, three additional 20-min clearances were then collected. Blood samples (approximately 100 μL) were collected after the first baseline clearance and at the conclusion of the study (approximately 500 μL); animals were euthanized by the injection of a lethal dose of sodium pentobarbital.

Protocol ii: Effects of Losartan and of Losartan plus LNA on GFR and MAP in Control and Diabetic Rats

To determine to what extent the RAS, or the RAS in combination with the NO system, is responsible for diabetes-related glomerular hyperfiltration, seven control and seven diabetic rats treated with losartan and then with losartan plus LNA were evaluated. As in Protocol i, if the elevated GFR in diabetic rats is caused by an increase in the activity of the RAS or by a combined alteration in the RAS plus the NO system, losartan or losartan plus LNA should normalize the GFR between control and diabetic rats. After surgery and a 30-min stabilization period, 2 × 20-min baseline clearances were collected. A bolus injection of losartan (1 mg/kg) was then administered, followed by a continuous infusion (50 μg/kg per min) for the remainder of the experiment. After 30 min, 2 × 20-min clearances were again collected. An infusion of LNA at 50 μg/kg per min plus losartan was then initiated and continued for the remainder of the experiment; after 60 min of losartan plus LNA, 3 × 20-min clearances were collected.

Protocol iii: Effect of Nephrectomy on LNA-Induced Increase in MAP in Control and Diabetic Rats

To determine to what extent the kidney participates in the systemic response to NO inhibition in control and diabetic rats, LNA was infused into six bilaterally nephrectomized control and six bilaterally nephrectomized diabetic rats. Immediately after the usual surgical procedures, the kidneys were isolated via an abdominal incision and a tight ligature was positioned around the renal pelvis; because no urine was formed in these experiments, both groups of rats received only an iv infusion of 24 μL/min. After a 20-min stabilization period, LNA was administered in the same manner as in intact control and diabetic rats. Arterial blood pressure changes were monitored for 90 min; the animals were then euthanized with a lethal dose of pentobarbital.

Analytical and Statistical Procedures

Urine volumes were determined gravimetrically. Creatinine concentrations in blood and urine were measured by the method of Folin and Wu (25); the clearance of creatinine was equated with the GFR (26).

Statistical differences of values within each group were determined by the use of a one-way analysis of variance for repeated measures and Duncan's new multiple-range test. Differences between groups were evaluated by use of a t test for grouped data. Values were accepted as significantly different when the probability of difference was less than 5%. Means ± SE are reported.

Drugs and Chemicals

Losartan was obtained from DuPont Merck Pharmaceutical Company (Wilmington, DE). All other chemicals were purchased from Sigma (St. Louis, MO).
RESULTS

Protocol I: Effects of LNA on GFR and MAP in Control and Diabetic Rats

The average body weights and kidney weights of control and diabetic rats in Protocol I are summarized in Table 1. There were no significant differences in body weights between the two groups. By contrast, the kidneys were significantly heavier in the diabetic rats compared with the control rats (P < 0.05). Blood glucose levels were substantially lower in control animals (110 mg/dL) than in diabetics (≥400 mg/dL).

Table 2 summarizes MAP, GFR, and urine flow rate values for the control and diabetic rats in Protocol I. There was no significant difference in the baseline MAP between control and diabetic rats. The infusion of LNA caused a significant increase in MAP in both groups (P < 0.05 compared with corresponding baseline values). The plateau value for MAP obtained during the infusion of LNA was significantly higher (P < 0.05) in controls compared with that of diabetic animals. However, as illustrated in Figure 1, the percent increase in MAP prompted by LNA was not significantly different between the two groups.

The baseline GFR, expressed in mL/min, was significantly higher (P < 0.05) in diabetic rats compared with controls. Moreover, as illustrated in Figure 2, the GFR, normalized per gram kidney weight, was also significantly higher in diabetics than in controls (P < 0.05). As is also illustrated in Figure 2, LNA caused a significant (P < 0.05) decrease in the GFR in only the control rats. Thus, the diabetes-related syndrome of hyperfiltration persisted during the infusion of the NO inhibitor.

Urine flow rate was significantly higher in diabetic (P < 0.05) compared with control rats (Table 2). Although the infusion of LNA resulted in an increase in urine flow rate above baseline in both groups, the increase was transient in the diabetic animals.

![Figure 1. Percent changes in MAP induced by LNA in control rats (open bars) and in diabetic rats (hatched bars) from Protocol I. * P < 0.05 compared with corresponding baseline.](image)

![Figure 2. LNA-induced changes in GFR, normalized per gram kidney, in control rats (open bars) and in diabetic rats (hatched bars) from Protocol II. * P < 0.05 compared with corresponding baseline; \( \ell P < 0.05 \) compared with corresponding control.](image)

TABLE 1. Body weights and kidney weights of rats in all protocols

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Body Weight (g)</th>
<th>Kidney Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol I</td>
<td>Controls (N = 8)</td>
<td>241 ± 15</td>
</tr>
<tr>
<td></td>
<td>Diabetics (N = 6)</td>
<td>259 ± 6</td>
</tr>
<tr>
<td>Protocol II</td>
<td>Controls (N = 7)</td>
<td>238 ± 8</td>
</tr>
<tr>
<td></td>
<td>Diabetics (N = 7)</td>
<td>235 ± 11</td>
</tr>
<tr>
<td>Protocol III</td>
<td>Controls (N = 6)</td>
<td>241 ± 8</td>
</tr>
<tr>
<td></td>
<td>Diabetics (N = 6)</td>
<td>238 ± 6</td>
</tr>
</tbody>
</table>

^a Values are mean ± SE.

^b P < 0.05 compared with corresponding controls.

Protocol II: Effects of Losartan and of Losartan plus LNA on GFR and MAP in Control and Diabetic Rats

The average body weights and kidney weights of rats from Protocol II are also summarized in Table 1. As was the case for rats in Protocol I, there were no significant differences in body weights between controls and diabetics in this group of rats. By contrast, the kidneys of the diabetic animals in Protocol II were again significantly heavier (P < 0.05) compared with controls. Blood glucose levels were substantially lower in control animals (110 mg/dL) than in diabetics (≥400 mg/dL).

MAP, GFR, and urine flow rate values of the rats from Protocol II are summarized in Table 3. Several points are important to note: (1) there was no significant difference between controls and diabetics for (a) the baseline MAP, (b) the MAP observed during treatment with losartan, or (c) the plateau MAP value.
observed during treatment with losartan plus LNA; (2) losartan had no effect on MAP in either group of rats; and (3) the percent increase in MAP prompted by LNA during treatment with losartan was the same in both groups. The latter fact is illustrated in Figure 3, a plot of the percent changes in MAP during the infusion of LNA in the presence of losartan. In addition, the percent changes in MAP values illustrated in this figure for controls and diabetics were not significantly different from the corresponding values obtained in Protocol i, i.e., animals treated with LNA alone.

Baseline and losartan GFR values were significantly higher in diabetics (P < 0.05) compared with controls (Table 3). As illustrated in Figure 4, during the infusion of losartan, the GFR, normalized per gram kidney weight, increased significantly in control (P < 0.05) but not in diabetic rats; nonetheless, the GFR per gram kidney weight remained significantly higher (P < 0.05) in diabetics compared with controls during treatment with losartan. In marked contrast, after the coinfusion of losartan and LNA, the GFR fell, significantly (P < 0.05), in the diabetic group but was unaffected in the control group. Consequently, after treatment with losartan plus LNA, the GFR values were not significantly different between the two groups, i.e., the diabetes-related syndrome of glomerular hyperfiltration was normalized by the coinfusion of the AngII receptor antagonist losartan plus the NO synthesis inhibitor LNA.

Urine flow rate was significantly lower in controls compared with diabetics (P < 0.05), however, there was no significant increase in flow rate after the coinfusion of losartan and LNA in either group. The increase in flow rate in control rats pretreated with losartan prompted by LNA was significantly greater compared with that in controls that received only LNA (P < 0.05); the increase in urine flow rate associated with LNA infusion was the same in diabetic rats with or without pretreatment with losartan.

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**Table 2. LNA-Induced Changes in Systemic and Renal Function of Rats in Protocol I**

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mm Hg)</th>
<th>Urine Flow Rate (µL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Control</td>
<td>Losartan</td>
</tr>
<tr>
<td></td>
<td>N = 8</td>
<td>N = 8</td>
</tr>
<tr>
<td>60 min</td>
<td>104 ± 7</td>
<td>138 ± 3</td>
</tr>
<tr>
<td>120 min</td>
<td>137 ± 3</td>
<td>140 ± 3</td>
</tr>
<tr>
<td>180 min</td>
<td>118 ± 3</td>
<td>118 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SEM. *P < 0.05 compared with corresponding control value.

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**Figure 3. Percent changes in MAP induced by losartan and then by losartan plus LNA in control rats (open bars) and in diabetic rats (hatched bars) from Protocol ii. * P < 0.05 compared with corresponding baseline.**
Losartan a

Figure 4. Losartan and losartan plus LNA-induced changes in GFR, normalized per gram kidney, in control rats (open bars) and in diabetic rats (hatched bars) from Protocol II. * P < 0.05 compared with corresponding baseline; † P < 0.05 compared with corresponding control; ‡ P < 0.05 compared with both corresponding baseline and losartan values.

Protocol iii: Effect of Nephrectomy on LNA-Induced Increase in MAP in Control and Diabetic Rats

The average body weights for nephrectomized control and diabetic rats are summarized in Table 1; the kidneys were not weighed in this group of rats. As in the other two protocols, the body weights were not significantly different between the two groups of rats in Protocol iii. Blood glucose levels were substantially lower in control animals (110 mg/dL) than in diabetics (≥400 mg/dL).

MAP values for rats in Protocol iii are summarized in Table 4. There were no significant differences in the baseline MAP between control and diabetic rats. The infusion of LNA caused a significant increase (P < 0.05) in MAP in both groups. Neither the plateau MAP values during the infusion of LNA, nor the percent increases in MAP prompted by LNA (illustrated in Figure 5), were significantly different between controls and diabetics.

Nephrectomized control and diabetic rats had significantly lower baseline MAP values compared with corresponding intact rats (P < 0.05). The plateau MAP values obtained during the infusion of LNA were significantly lower in nephrectomized controls when compared with intact controls (P < 0.05), but there was no difference in these values among the three groups of diabetic rats. Nonetheless, the fractional increase in MAP, illustrated in Figure 5, was significantly greater in both control and diabetic nephrectomized rats compared with corresponding intact rats (P < 0.05).

DISCUSSION

The goal of this study was to determine to what extent, under steady-state conditions, NO and/or the RAS contribute to the hyperfiltration observed in rats with STZ-induced diabetes mellitus. NO inhibition
with LNA with or without the AngII receptor antagonist losartan caused similar increases in MAP in control and diabetic animals. Moreover, after the inhibition of NO synthesis, the GFR, even when factored by kidney weight, remained significantly higher in diabetic rats compared with control rats, indicating that NO alone does not account for the hyperfiltration observed in diabetes mellitus. Similarly, glomerular hyperfiltration persisted in diabetics compared with control rats during treatment with losartan, indicating that changes in the activity of the RAS alone cannot account for diabetes-induced hyperfiltration. By contrast, during the infusion of LNA plus losartan, the GFR was not significantly different between control and diabetic rats. Thus, these data indicate that although neither changes in NO synthesis nor changes in the activity of the RAS alone can explain the glomerular hyperfiltration observed in diabetes mellitus, a combined difference in these two systems may contribute to the development of this syndrome.

The syndrome of glomerular hyperfiltration that occurs shortly after the onset of diabetes mellitus has long been recognized (27,28); however, the mechanism(s) responsible for this phenomenon remains unknown. Bank and Aynedjian reported that diabetic rats have an increased production of NO and that the inhibition of NO synthesis normalizes the GFR, indicating that hyperfiltration in the diabetic state is due to enhanced NO production (5). Similar results have also been reported by Tolins et al. (6) and by Komers et al. (7). By contrast, data from our study illustrate that in rats maintained in fluid balance and given a constant infusion of LNA, the GFR, expressed in absolute values or when normalized per gram kidney, remains elevated during the infusion of the NO inhibitor. Thus, regardless of whether or not NO production is increased, data from our study indicate that disturbances in NO synthesis and/or responsiveness alone do not appear to be the cause of hyperfiltration in the diabetic rat.

There are significant differences in the methods used in our study and those used by other groups that could account for these different results. Bank and Aynedjian (5) utilized repeated intra-arterial bolus injections of different concentrations rather than a continuous infusion of LNA and did not utilize fluid replacement in the group of diabetic rats. Tolins et al. (6) utilized an intrarenal infusion of N\textsuperscript{\textbf{\textdagger}}-nitro-L-arginine methyl ester (L-NAME) in rats after 6 wk of STZ-induced diabetes mellitus; furthermore, these rats were treated with insulin on a daily basis. Komers et al. (7) utilized an intravenous bolus injection of L-NAME into conscious, chronically instrumented rats 3 wk after the induction of diabetes mellitus with STZ. In our study, a constant intravenous infusion of LNA was utilized and rats were maintained in fluid balance with saline replacement. Thus, data from our study are likely to reflect steady-state values rather than transient estimates of physiologic variables. In addition, because rats in our study were in a state of fluid balance, changes elicited by the infusion of LNA and LNA plus losartan are not artificially altered by a state of dehydration.

Several authors have reported that the response to endothelium-dependent vasodilation is disrupted in various vascular beds in diabetic rats. Kiff et al. (9) reported that in STZ-induced diabetic rats, there is an attenuated vasoconstriction in the hindquarter vascu-
lar bed during NO inhibition; they did not observe any
difference in the renal or mesenteric response between
diabetic and control animals. However, Wang et al.
(10) reported an attenuation in the renal vasodilatory
response to acetylcholine in STZ-induced diabetic rats
and attributed this to a decrease in the production of
endothelium-dependent relaxing factor/NO or a de-
fective soluble guanylate cyclase. Furthermore, May-
han (11) determined that a diminished endothelium-
dependent vasodilation in the basilar artery of
diabetic rats is not a result of the activation of the
thromboxane A₂-prostaglandin H₂ receptor. Using
WBN/Kob rats, a strain that is genetically diabetic,
Miyata et al. (29) also showed that there is impaired
endothelium-dependent vasodilation in the thoracic
aorta and mesenteric arteries compared with control
rats. Data from the study presented here indicate that
the MAP response to NO inhibition is the same in both
diabetic and control animals, demonstrating that al-
though endothelium-dependent vasodilation in indi-
vidual arterial beds may differ between the two
groups, the MAP response to NO inhibition is not altered in diabetic animals.

It has been reported that the RAS is depressed,
normal, or even elevated in the STZ-induced diabetic
rat (30–33). Abnormalities in the intrarenal RAS have
been described by several authors. Remuzzi et al. (34)
demonstrated that losartan completely abolished a
diabetes-induced increase in glomerular membrane
pore size and subsequent proteinuria and glomerulo-
sclerosis. Furthermore, Remuzzi et al. (34) and Ander-
sen et al. (16) found an increase in the intrarenal
content of renin, angiotensinogen mRNA, and renin
(16) found no difference in plasma renin concentra-
tions or ACE activity between control and diabetic
rats. By contrast, Kalinyak et al. (15) found that
although there were neither differences in plasma
renin concentrations nor differences in intrarenal lev-
eels of angiotensinogen and renin mRNA between con-
trol and diabetic rats, the number of renal AngII
receptors was reduced in diabetic animals. Further-
more, in the diabetic rats, ACE activity was increased
in both glomeruli and the renal vasculature.

Sigmon et al. (17,18) and Takenaka et al. (19) have
demonstrated that AngII causes decreases in RBF,
GFR, and sodium excretion in LNA-treated rats. Both
groups concluded that tonically released NO may
serve as an inhibitory modulator of AngII in vivo. How-
ever, in another study, Sigmon et al. (35) found that
in barbiturate-anesthetized rats, PRA is two to three
times that observed in conscious rats. They conclud-
ed that when the vasoconstrictive action of
AngII is increased, NO has a more important role as a
counterbalancing agent, causing the LNA-induced
decrease in GFR to be AngII mediated. In a study utiliz-
ing chronically instrumented conscious rats, Sigmon
et al. (36) demonstrated that NO inhibition results in
an AngII–mediated decrease in RBF independent of
the systemic response. Ito et al. (37) corroborated
these results and further demonstrated that NO mod-
ulates the constrictor action of AngII in afferent but
not efferent arterioles, accounting for the greater sen-
sitivity of the efferent arteriole to AngII.

An important finding of our study is that losartan
induces a hyperfiltration in control rats and a result-
ant attenuation of the LNA-induced decrease in GFR.
These data suggest that AngII production may ac-
count for the LNA-induced decrease in GFR in anes-
thetized control rats; however, this may be due to a
barbiturate-induced increase in PRA, as suggested by
Sigmon et al. (35) and Baylis et al. (20). On the other
hand, losartan-treated diabetic rats have an exagger-
ated GFR response to the NO inhibitor. Although an
explanation for the contrasting results will require
additional studies, it does appear that a combination
of alterations in both the NO system and the RAS in
diabetic rats may account for the hyperfiltration ob-
erved in this disorder.

The interaction between the RAS and NO and its
effects on MAP have been investigated by many
groups, often with conflicting results. Pollock et al.
(21) and Jover et al. (22) have shown that the hyper-
tension induced by long-term NO inhibition can be
abolished by the simultaneous infusion of losartan.
However, Sigmon et al. (17,18) and Takenaka et al.
(19) demonstrated that AngII does not contribute to
the increase in systemic blood pressure in rats acutely
treated with LNA. The results of our study confirm
and extend those from acute studies in the control rat
to the diabetic rat.

The experiments with anephric rats were used to
determine to what extent renal factors, in addition to
AngII, are involved in the systemic response to NO
inhibition in control and diabetic rats. Because there
was a greater fractional increase in MAP in these rats
compared with intact animals, these data indicate that
there is a small renal involvement in the systemic
response to NO inhibition. Whether this enhanced
response is related to the release of other vasoactive
agents from the kidney during treatment with LNA or
to other factors will require additional experiments.
What is clear, however, is that vasoconstrictive sub-
stances of renal origin are not necessary for the in-
crease in MAP induced by the inhibition of NO in either
control or diabetic rats.

In summary, data from our study indicate that the
increase in GFR observed in rats 7 to 10 days after
STZ-induced diabetes mellitus cannot be attributed to
changes in either the NO system or the RAS alone but
may involve a combined change in both of these
physiologic variables. By contrast, the increase in
MAP induced by the inhibition of NO synthesis is not
altered in this model of diabetes nor is the MAP
response dependent on AngII or on other vasocon-
strictive agents of renal origin in controls or diabetics.

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