Renal Responses to Intra-arterial Administration of Nitric Oxide Donor in Dogs

Dewan S.A. Majid, Anita Williams, Philip J. Kadowitz, L. Gabriel Navar

Inhibition of nitric oxide synthesis by intra-arterial administration of nitro-L-arginine (NLA) leads to attenuation of the slope of the relation between renal arterial pressure (RAP) and sodium excretion without an alteration in renal autoregulatory efficiency. In the present study, we examined whether only the presence of nitric oxide or, alternatively, changes in nitric oxide production during changes in RAP are required for pressure natriuresis to occur. Anesthetized sodium-replete dogs (n=8) were treated with NLA (50 μg · kg⁻¹ · min⁻¹) to inhibit endogenous nitric oxide formation, and S-nitroso-n-acetylpenicillamine (SNAP) was infused intra-arterially at a constant rate (2 μg · kg⁻¹ · min⁻¹) to replenish intrarenal nitric oxide levels. Renal responses to reductions in RAP within the autoregulatory range were assessed before and during NLA infusion followed by SNAP+NLA infusion. As reported previously, NLA infusion alone increased renal vascular resistance and decreased renal blood flow, urine flow, sodium excretion, and fractional excretion of sodium, with no change in glomerular filtration rate. Autoregulatory efficiency remained intact, whereas the pressure-induced natriuretic responses were attenuated. During SNAP+NLA infusion, renal blood flow increased from 2.8±0.3 to 3.5±0.3 mL · min⁻¹ · g⁻¹ (P<0.001), without significant changes in glomerular filtration rate (0.75±0.07 to 0.81±0.05 mL · min⁻¹ · g⁻¹); the autoregulatory efficiency of renal blood flow and glomerular filtration rate remained intact. SNAP increased urine flow (4.8±1.8 to 10.0±2.5 μL · min⁻¹ · g⁻¹), sodium excretion (0.63±0.16 to 1.70±0.37 μmol · min⁻¹ · g⁻¹), and fractional excretion of sodium (0.55±0.20% to 1.38±0.27%). Despite the natriuresis induced by SNAP, the slope of the relation between sodium excretion and RAP remained attenuated. These data support the concept that alterations in intrarenal nitric oxide production during changes in RAP participate in the mediation of pressure natriuresis.

KEY WORDS • hemodynamics • autoregulation • arginine • nitric oxide • natriuresis

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understood but could be due to the influence of the
associated increase in arterial pressure or other mechan-
isms that are activated by systemic administration of
L-arginine analogues. Nevertheless, inhibition of NO
synthesis by intrarenal administration of NLA leads to a
marked attenuation of the urine flow and sodium excre-
tory responses to changes in renal arterial pressure
(RAP) without any effect on the autoregulatory capa-
ability of renal blood flow (RBF) and GFR, suggesting
that NO exerts either a permissive or a mediatory role
in pressure natriuresis.9,11

The present investigation was carried out to deter-
mine whether simply the presence of NO in contrast to a
change in NO production during changes in RAP is
required for pressure natriuresis to occur. For this
study, we used S-nitroso-N-acetylpenicillamine (SNAP),
an S-nitrosothiol known to be a potent in vivo vasodilat-
tor.16 SNAP was infused intrarenally at a constant rate
in anesthetized dogs in which endogenous NO synthesis
was inhibited by the administration of NLA. The objec-
tive was to achieve a relatively constant level of intra-
renal NO levels during changes in RAP under condi-
tions in which the renal capability to form endogenous
NO was blocked.

**Methods**

Experiments were carried out in eight mongrel dogs
(20.8±0.6 kg body wt) of either sex. The preparation of
the animals and basic experimental techniques are
similar to those previously described.9 To achieve a
positive sodium balance and stimulate a physiological
natriuresis, we added supplemental amounts of sodium
chloride (1.5 g/kg body wt per day for 3 days) to the
normal laboratory diet. On the morning of the experi-
mental day, the dogs were anesthetized with pentobar-
bital sodium (30 mg/kg body wt IV); surgical anesthe-
thesia was maintained throughout the experiment by addi-
tional doses of pentobarbital sodium as required (ap-
proximately 4 mg·kg⁻¹·h⁻¹). Auffed endotracheal
tube was inserted into the trachea to allow positive
pressure ventilation with an artificial respirator at a
stroke rate of 18/min and stroke volume of approxi-
mately 15 mL/kg body wt. Body temperature of the
animal was measured continuously by a telethermome-
ter placed in the rectum and was maintained within the
normal range with an electric heating pad placed under
the dog.

Systemic arterial pressure of these dogs was mea-
sured from a catheter placed in the abdominal aorta
inserted via the right femoral artery and connected to a
pressure transducer and was recorded on a polygraph
(model 7D, Grass Instrument Co, Quincy, Mass). At
least 30 minutes before the experimental protocol was
started, dogs were subjected to occlusion of the right
common carotid artery with partial constriction of the
left common carotid artery in order to elevate the basal
level of arterial pressure to approximately 150 mm Hg.
This procedure allowed evaluation of the relation be-
tween renal perfusion pressure and Uₐ • V over a wider
range of arterial pressure. The left femoral artery was
cannulated for collection of blood samples. The femoral
and jugular veins were cannulated for administration of
an inulin solution and additional doses of pentobarbital
sodium as necessary. During the entire experimental
period, dogs were given a continuous infusion of iso-
tonic sodium chloride solution (0.9%) at a rate of 0.025
mL·min⁻¹·kg⁻¹ via a catheter placed in the right femoral
vein.

The left kidney was exposed through a flank incision,
and the renal artery was isolated from surrounding
tissue. The kidney was denervated by cutting the renal
nerves. RBF was measured with an electromagnetic
flow probe placed on the renal artery near its origin
from the aorta and connected to a square wave flowme-
ter (Carolina Medical Electronics, King, NC). The flow
traces were recorded on the polygraph, and zero-flow
baseline was determined at the beginning and end of
each experiment by momentarily occluding the artery.
An adjustable plastic clamp was placed around the renal
artery distal to the flow probe to achieve reductions in
RAP. A curved 23-gauge needle cannula was inserted
into the renal artery distal to the plastic clamp and was
connected to another pressure transducer with a poly-
ethylene catheter to measure RAP. Another catheter
was also connected to this needle cannula for continu-
ous infusion of heparinized saline at a rate of 0.4
mL/min to prevent any clot formation and to allow
intrarenal administration of drugs (NLA and SNAP).
Drugs were dissolved in the heparinized saline, and the
concentrations were adjusted to maintain the same
volume infusion rate (0.4 mL/min). Urine was collected
into a graduated test tube from a catheter placed in the
ureter.

After completion of all surgical procedures, a 2.5%
solution of inulin in normal saline was administered via
a catheter placed in the left jugular vein. A priming dose
of 1.6 mL/kg body wt of inulin solution was followed by a
sustaining infusion of 0.03 mL · min⁻¹ · kg⁻¹ body wt.
At least 45 minutes was allowed between the initiation
of the inulin infusion and the start of control hemody-
namic measurements and urine collections. The experi-
mental protocol started with urine collections for two
consecutive 10-minute periods at a spontaneous RAP of
approximately 150 mm Hg. At the midpoint of each
urine collection period, an arterial blood sample (2 mL)
was taken to measure plasma inulin, sodium, and potas-
sium concentrations. After control measurements at
spontaneous arterial pressure, step reductions in RAP (ap-
proximately 125, 100, and 75 mm Hg) were produced
by adjusting the clamp. At each level of RAP, at least 5
minutes was allowed for stabilization before a 10-
minute urine collection was made. Below 75 mm Hg of
arterial pressure, RAP was further reduced in steps of
15 to 20 mm Hg for 2 to 3 minutes in each step until
RBF was reduced to near zero. After the last reduction
in RAP, the clamp was released completely to reestab-
lish control RAP and RBF. After control measure-
ments, a continuous infusion of NLA (Aldrich Chemical
Co Inc, Milwaukee, Wis; dissolved in heparinized nor-
mal saline, wt/vol; pH 6.8±0.3) was initiated at a rate of
0.03 mL · min⁻¹ · kg⁻¹ intrarenally. This dose of NLA was
previously reported to yield an effective blockade of
endogenous NO activity in the kidney.9 Thirty minutes
after the initiation of the NLA infusion, the same
protocol was repeated to examine pressure-related re-
sponses during NO synthesis inhibition.

After reestablishment of control RAP and RBF at the
end of the experimental protocol with NLA infu-
sion, a continuous intrarenal infusion of SNAP (2
µg · kg⁻¹ · min⁻¹; provided by Dr Louis J. Ignarro, De-
Renal Responses to Intra-arterial Infusion of S-Nitroso-n-Acetylpenicillamine In Dogs (n=8) Treated With Nitro-l-Arginine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>NLA</th>
<th>SNAP+NLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure, mm Hg</td>
<td>152±4.6</td>
<td>159±4.8</td>
<td>148±5.4*</td>
</tr>
<tr>
<td>RVR, mm Hg · mL⁻¹ · min⁻¹ · g⁻¹</td>
<td>36.7±2.4</td>
<td>57.6±3.8f</td>
<td>43.5±3.3*</td>
</tr>
<tr>
<td>RBF, mL · min⁻¹ · g⁻¹</td>
<td>4.14±0.38</td>
<td>2.76±0.26t</td>
<td>3.50±0.32*</td>
</tr>
<tr>
<td>GFR, mL · min⁻¹ · g⁻¹</td>
<td>0.86±0.06</td>
<td>0.75±0.07</td>
<td>0.81±0.05</td>
</tr>
<tr>
<td>Urine flow, µL · min⁻¹ · g⁻¹</td>
<td>16.1±5.3</td>
<td>4.8±1.8f</td>
<td>10.0±2.5*</td>
</tr>
<tr>
<td>U_NaV, µmol · min⁻¹ · g⁻¹</td>
<td>3.00±0.72</td>
<td>0.63±0.26f</td>
<td>1.70±0.37*</td>
</tr>
<tr>
<td>FENa, %</td>
<td>2.24±0.43</td>
<td>0.55±0.20f</td>
<td>1.38±0.27*</td>
</tr>
<tr>
<td>U_KV, µmol · min⁻¹ · g⁻¹</td>
<td>0.57±0.14</td>
<td>0.38±0.08f</td>
<td>0.73±0.12*</td>
</tr>
</tbody>
</table>

NLA indicates nitro-l-arginine; SNAP, S-nitroso-n-acetylpenicillamine; RVR, renal vascular resistance; RBF, renal blood flow; GFR, glomerular filtration rate; U_NaV, urinary sodium excretion; FENa, fractional excretion of sodium; and U_KV, urinary potassium excretion. Data are expressed as mean±SEM.

*P<.05 vs NLA.
†P<.05 vs control.

The effects of intra-arterial infusion of the cold solution of saline vehicle on renal hemodynamics and renal excretory values were assessed in three NLA-treated dogs. After two consecutive 10-minute urine-collection periods with intrarenal infusion of vehicle at room temperature, a cold solution of the saline vehicle (syringe jacketed with ice as in SNAP infusion) was initiated. Fifteen minutes after the initiation of the cold solution, another set of 10-minute urine samples was collected. It was observed that infusion of cold saline intrarenally at the low infusion rate used to deliver the drugs did not perceptibly change the basal level of renal parameters measured in this study.

At the end of each experiment, the flow probe was calibrated in situ by collection of timed blood samples at different flow rates into a graduated cylinder from a catheter placed in the renal artery. The kidney was then removed, stripped of all surrounding tissue, blotted dry, and weighed so that the calculated values could be expressed per gram of net kidney weight. Flame photometry (Instrumentation Laboratories, Lexington, Mass) was used to determine the sodium and potassium concentrations in plasma and urine. Inulin concentrations in plasma and urine samples were determined by the anthrone colorimetric technique. GFR was calculated with standard inulin clearance techniques. Microhematocrit measurements were performed on all arterial blood samples. Values are reported as mean±SEM. Statistical comparisons of differences in the responses were conducted with analysis of variance for repeated measures followed by the Newman-Keuls test. Differences in the mean values were deemed significant at a value of P≤.05. The RBF autoregulation curve was generated by extrapolating the values of RBF at different levels of RAP (at 25 mm Hg intervals ranging from 150 to 25 mm Hg). Two separate linear regression analyses of the pressure-flow relations were carried out in each dog to obtain the extrapolated values: at the pressure levels at which RBF was autoregulated and at lower pressures at which a linear relation between RAP and RBF was obtained. RBF was considered autoregulated when the RBF values remained within 5% of the control RBF. The RAP versus RVR relation curve was also generated by extrapolating the values of RVR at different levels of RAP as in autoregulation curves.

Results

After stabilization of the preparation, the mean values of plasma sodium, potassium, and hematocrit during the control periods were 147±1.4 mmol/L, 3.5±0.1 mmol/L, and 43.7±2.7%, respectively. These values did not change significantly during infusion of NLA (147±1.3 mmol/L, 3.6±0.2 mmol/L, and 42.3±3.4%) or SNAP+NLA (148±1.4 mmol/L, 3.7±0.1 mmol/L, and 42.1±3.5%).

Effect of SNAP Infusion on Basal Level of Renal Hemodynamics and Function in NLA-Treated Dogs

The Table summarizes the results obtained in the eight study dogs. Control arterial pressure was elevated to 152±5 mm Hg because of the partial constriction of the carotid arteries. This effect waned slightly during the course of the experiment but returned to this range during NLA infusion (159±5 mm Hg). NLA infusion alone resulted in an increase of 58±7% in RVR and decreases of 33±3% in RBF, 68±5% in urine flow, 84±4% in U_NaV, 80±5% in fractional excretion of sodium (FENa), and 31±8% in urinary potassium excretion (U_KV). There was a slight but statistically insignificant decrease in GFR (-12±7%) during NLA administration. These findings...
are similar to our earlier reported observations in salt-replete anesthetized dogs. Addition of SNAP (2 μg · kg⁻¹ · min⁻¹) to the intrarterial infusion line for more than 15 minutes partially reversed the effects caused by infusion of NLA alone. Systemic arterial pressure and RAP decreased gradually starting 3 minutes after the onset of the SNAP infusion. Administration of SNAP for more than 15 minutes led to decreases in systemic arterial pressure from 159±5 to 149±5 mm Hg (P<.05). RBF increased consistently and started to increase within 2 minutes of infusion and reached its near maximum peak within 5 minutes of SNAP infusion. The Table summarizes the results obtained at steady state after combined SNAP and NLA infusion for 15 minutes. As noted in the Table, during combined infusion there were significant decreases in RVR and increases in RBF, U₁⁵,V, FE₉⁵, and U₉⁵ from the levels obtained during NLA infusion alone. The slight increase in the mean value of GFR during addition of SNAP from the mean value during infusion of NLA alone was not statistically significant. Comparatively larger relative increases in U₁⁵,V than U₉⁵ during SNAP infusion were also noted in these dogs.

Effect of SNAP Infusion on Renal Autoregulation

Figs 1 and 2 illustrate the effect of SNAP infusion on autoregulatory efficiency of RBF and GFR in NLA-treated dogs. As reported earlier, autoregulatory efficiency of RBF and GFR remained intact during NLA infusion alone; however, there was a leftward shift of the RAP versus RVR relation curve during NLA infusion (Fig 1B) due to increases in RVR to NLA treatment, as reported previously. The autoregulation plateau of RBF was lowered, without any significant change in the slope of the autoregulatory portion of the curve during infusion of NLA alone (Fig 1A). Also, the slope of the linear portion of the RBF autoregulation curve below 75 mm Hg was slightly decreased during NLA treatment (0.07±0.01 to 0.04±0.01 mL · min⁻¹ · mm Hg⁻¹; P<.01). GFR remained well autoregulated at a mean RAP above 75 mm Hg in NLA-treated dogs (Fig 2A), without any significant change in the slope of the relation between RAP and GFR.

After administration of SNAP to NLA-treated dogs, the basic pattern of autoregulatory efficiency of RBF and GFR remained intact (Figs 1 and 2). The RBF autoregulation plateau was partially restored toward control level during SNAP treatment. Interestingly, RBF autoregulatory efficiency was slightly augmented, with slight increases in RBF at the lower arterial pressures during SNAP infusion. As a result, there was a slight but significant change in the mean slope of the autoregulatory portion of the curves from the NLA infusion period to the SNAP + NLA infusion period (0.002±0.01 to -0.007±0.001 mL · min⁻¹ · g⁻¹ · mm Hg⁻¹; P<.01). The slopes of the linear portion of the curves at RAP below 75 mm Hg increased during SNAP treatment compared with the NLA infusion period (0.08±0.01 mL · min⁻¹ · g⁻¹ · mm Hg⁻¹; P<.01). However, the autoregulatory efficiency of GFR at a mean RAP above 75 mm Hg remained intact during SNAP treatment, as in both control and NLA treatment periods (Fig 2A). As SNAP administration caused reductions in RVR, the RBF versus RVR relation curve during the NLA treat-
ment period shifted to the right toward the control curve during the SNAP period (Fig 1B).

Effect of SNAP on Renal Excretory Responses to Reductions in Renal Arterial Pressure

Fig 2 illustrates the effects of SNAP infusion on pressure-induced changes in excretory function of the kidney. As reported earlier, there was a marked attenuation of urine flow (Fig 2B), U_{NaV} (Fig 3A), and FENa (Fig 3B) responses to changes in RAP during NLA treatment. The slope of the RAP versus urine flow relation was significantly reduced, from 0.16±0.05 to 0.014±0.01 µL·min^{-1}·g^{-1}·mm Hg^{-1} (P<.01), during NLA infusion alone. The slopes of the RAP versus U_{NaV} and RAP versus FENa relations were also reduced, from 0.03±0.01 to 0.01±0.002 µmol·min^{-1}·g^{-1}·mm Hg^{-1} (P<.01) and from 0.03±0.005 to 0.004±0.002 %·mm Hg^{-1} (P<.01), respectively, during NLA infusion. These responses are consistent with our earlier reported observations in sodium-replete dogs. After addition of SNAP, the values of urine flow, U_{NaV}, FENa, and U_{NaV} at a spontaneous level of RAP increased from the values during NLA infusion alone (Table). Nevertheless, the excretory responses to reductions in RAP remained attenuated, as was observed during NLA treatment alone (Figs 2 and 3). There were no significant changes in the slopes of RAP versus urine flow (0.014±0.001 to 0.04±0.013 µL·min^{-1}·g^{-1}·mm Hg^{-1}) and RAP versus U_{NaV} (0.01±0.002 to 0.01±0.003 µmol·min^{-1}·g^{-1}·mm Hg^{-1}) during addition of SNAP. The slope of RAP versus FENa also remained the same as during NLA infusion alone (0.004±0.002 to 0.008±0.002 %·mm Hg^{-1}). Thus, the slope of the pressure-natriuresis relation remained markedly attenuated even though the absolute excretion rates were elevated by the SNAP.

Discussion

The present investigation demonstrates that direct infusion of the NO donor SNAP into the renal artery in anesthetized dogs in which endogenous NO synthesis was inhibited with NLA elicited vasodilator and natriuretic responses in the kidney. There were decreases in RVR and increases in RBF, urine flow, and U_{NaV} without significant changes in GFR. We have also observed that these responses to SNAP administration were dose dependent. As NO generation is the essential effector of the mechanism of action of nitrovasodilators, and the biologic actions of S-nitrosothiols such as SNAP are attributed to NO, the renal responses to SNAP infusion observed in these experiments are most likely due to the intrarenal actions of NO. S-Nitrosothiols were previously proposed to be active intermediates in mediating the vascular smooth muscle relaxant actions of nitrovasodilators. However, it has been shown that nitrovasodilators generate NO, and such generation is responsible for the activation of soluble guanylate cyclase. As S-nitrosothiols are very unstable, especially at physiological pH and temperature, and spontaneously release NO and activation of guanylate cyclase by NO can occur without the presence of thiols, it is now believed that NO is the final active principle in the mechanism of actions of S-nitrosothiols in guanylate cyclase activation. It has been shown recently that vasodilator responses to SNAP and NO are inhibited in a similar manner in vivo by methylene blue, an inhibitor of soluble guanylate cyclase, indicating that SNAP releases NO and activates soluble guanylate cyclase.

The basal level of arterial pressure was elevated to approximately 150 mm Hg by partial occlusion of the carotid arteries in these experiments. This procedure might influence the subsequent responses to NLA and SNAP. However, because the kidney was denervated, it is unlikely that the observed renal responses to NLA and SNAP infusion were influenced by neurohumoral factors that could appear as a consequence of carotid occlusion. Previous studies have indicated that the secretion of catecholamines (epinephrine and norepinephrine) from the adrenal medulla was relatively unaffected by bilateral carotid occlusion in conscious dogs. Although the neural modulation of NO activity is a subject of recent interest, at present there is no evidence to suggest that the effects of NO will be different in innervated kidneys.

Although SNAP elicited renal vasodilation, autoregulatory efficiency of RBF and GFR remained intact during SNAP administration. There was a significant leftward shift toward control in the slope of the linear portion of the pressure-flow curve during SNAP infusion in NLA-treated dogs. These findings further support our earlier conclusions that NO primarily influences an autoregulatory-independent component of RVR. Consistent with the findings during inhibition of

Fig 3. Line graphs showing sodium excretion (UNaV) (A) and fractional excretion of sodium (FENa) (B) responses to acute changes in renal arterial pressure (RAP) above 75 mm Hg before (○) and during (●) nitro-l-arginine (NLA) infusion and during (△) infusion of S-nitroso-n-acetylpenicillamine (SNAP) + NLA (n=8). Responses to reductions in RAP remained attenuated during SNAP infusion as during NLA infusion. Error bars indicate SEM.
endogenous NO production in anesthetized dogs, exogenous NO administration in these experiments also failed to elicit changes in GFR. These findings are consistent with the concept that NO exerts a proportionate influence on both preglomerular and postglomerular resistance segments. 9-22-33 This suggests a more direct action of NO on tubular sodium reabsorptive processes in the kidney. 9,11 However, these data do not provide further clarification of the mechanism involved in NO-induced changes in tubular reabsorptive function, which may be due to a direct inhibitory action of NO on epithelial sodium transport 29 or may occur as a consequence of an altered intrarenal hemodynamic environment. 30-32 Further studies are required to elucidate the exact mechanism and the nephron segments responsible for NO-induced inhibition of tubular sodium reabsorption.

As reported earlier, 6 NLA administration in anesthetized sodium-replete dogs in this study resulted in marked attenuation of the urine flow and sodium excretory responses to reductions in RAP. Although there was a partial restoration in the magnitude of UNoV after addition of SNAP, the excretory responses to reductions in RAP remained attenuated during SNAP application. At lower doses of SNAP, which were not used in this study to avoid large changes in systemic pressure. This is an obvious problem in studies involving intra-arterial infusion, which leads to substrate overflow and loss of agent to the circulation.

A constant infusion of exogenous NO in the renal artery in these NLA-treated dogs failed to increase the slopes of the relations between arterial pressure and UNoV or FEoV. These interesting findings suggest that a simple absence of NO in the NLA-treated dogs was not the cause of attenuation in the pressure-induced natriuretic responses. The replenishment of NO in these NLA-treated dogs reversed UNoV toward control levels, yet the pressure-natriuresis curve remained attenuated, as during NLA infusion alone. This pattern is clearly different from those previously observed in response to other vasodilator or natriuretic agents that have usually caused a marked augmentation of the slope of the pressure-natriuresis relation. 9,22-23 This suggests a more direct association between NO and the mechanism responsible for pressure natriuresis.

From the present study we cannot determine the amount of NO delivered intrarenally by the administered dose of SNAP or the actual intrarenal NO levels. Considering the magnitude of the sodium excretory responses to changes in RAP, it may be assumed that the intrarenal NO levels achieved were similar to those present in the kidney at RAP levels of approximately 100 mm Hg before NO blockade. These results indicate that the amounts of endogenous NO present in the kidney at a RAP of 125 or 150 mm Hg during the control period were more than the amount of NO delivered by the SNAP infusion. This suggests that increases in RAP under control conditions increase endogenous NO production in the kidney. Thus, these data support the hypothesis that an alteration in the formation and release of NO by endothelial cells occurs in response to changes in RAP and may be an essential component of the mechanism responsible for pressure-induced diuretic and natriuretic responses in the kidney. 5 Further studies will be required to quantify the intrarenal NO activity at different levels of arterial pressure and to examine the causal relation between such NO activity and observed changes in UNoV.

In conclusion, the results of the present investigation demonstrate specific actions of NO to elicit renal vasodilation and natriuresis. Furthermore, these data suggest that alterations in intrarenal NO activity during changes in arterial pressure are requisite for full expression of pressure-natriuretic responses.

Acknowledgments

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References


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