Inhibition of Nitric Oxide, Bradykinin, and Prostaglandins in Normal Rats

Yi-Xin Wang, Irene Gavras, Tomasz Wierzba, Bernard Lammek, and Haralambos Gavras

We assessed the vasodilator effect of endothelium-derived nitric oxide by inhibiting its formation with N\textsuperscript{\textcircled{2}}-monomethyl L-arginine (LNMMA) on systemic and regional hemodynamics in conscious, normotensive rats, using the radioactive microsphere technique. In rats injected with 10 mg/kg LNMMA (n=8), mean blood pressure increased by 16.2±2.6 mm Hg, and heart rate decreased by 54.3±16.7 beats per minute. In comparison with rats injected with 5% dextrose (n=14), cardiac index was lower by 35.6% (p<0.01), and total peripheral vascular resistance was higher by 51.6% (p<0.01); regional blood flows were lower and vascular resistance higher in most organs. Changes were significant in the heart, kidney, stomach, large intestine, skin, and adrenals (p<0.05). Preinjection of 100 mg/kg L-arginine prevented the pressor response but only partially attenuated the other hemodynamic effects of LNMMA. Combination of LNMMA with the bradykinin antagonist (D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Phe-Thi-Arg)trifluoroacetic acid (50 μg/min for 5 minutes) did not produce systemic or regional effects different from those obtained with LNMMA alone. Combination of LNMMA with indomethacin (10 mg/kg) resulted in additional changes in the cerebral circulation, blood flow decreasing by an additional 44.2% (p<0.01) and vascular resistance increasing by 753% (p<0.01) compared with changes produced by LNMMA alone. The data suggest that endothelium-derived nitric oxide contributes differently to the resting vascular tone of various vascular beds; it mediates most of the vasodilator effects of bradykinin and partly those of prostaglandins, but the effect of the latter on the cerebral circulation is not nitric oxide dependent. (Hypertension 1992;19[suppl II]:II-255–II-261)

From the Hypertension Section and Department of Medicine, Thorside Memorial Laboratory, Boston City Hospital and the Department of Medicine, University Hospital, Boston University School of Medicine, Boston, Mass.

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Address for correspondence: Haralambos Gavras, MD, Hypertension and Atherosclerosis Section, Boston University Medical Center, 80 East Concord Street, L-217, Boston, MA 02118.

Endothelium-derived relaxing factor (EDRF) is a vasodilator substance generated by endothelial cells within the vessel wall. Many vasodilators, such as bradykinin, acetylcholine, and substance P, induce relaxation of isolated vascular tissue by release of EDRF\textsuperscript{1,2} and therefore are called endothelium-dependent vasodilators. Recent evidence indicates that the main EDRF is nitric oxide\textsuperscript{3–11} and that its biosynthetic precursor is L-arginine.\textsuperscript{10,12} N\textsuperscript{\textcircled{2}}-Monomethyl L-arginine (LNMMA) was found to inhibit vascular nitric oxide production in endothelial cells and thus inhibit relaxation induced by endothelium-dependent vasodilators both in vitro\textsuperscript{12,13} and in vivo.\textsuperscript{14,15} Inhibition of the endothelium-derived nitric oxide formation by LNMMA increased blood pressure in anesthetized rabbits,\textsuperscript{14} rats,\textsuperscript{15} and guinea pigs\textsuperscript{16} and decreased forearm blood flow in humans.\textsuperscript{17} Recently, Gardiner et al\textsuperscript{18} reported that LNMMA caused vasoconstriction in the internal carotid, mesenteric, renal, and hindquarters vascular beds. However, the in vivo sensitivity of the vasculature of other organs to the vasorelaxant effect of EDRF and thus the role of EDRF in the regulation of regional blood flows, especially the coronary vasculature under physiological conditions, remains unknown. On the other hand, although LNMMA was also found to modulate the systemic vasodepressor effect of exogenous bradykinin but not of prostacyclin,\textsuperscript{15} its relation to endogenous bradykinin or prostaglandins in the regulation of regional blood flows is still unclear.

The purpose of the present study was to further explore the role of nitric oxide in maintaining resting vascular tone and in mediating the systemic and regional vasodilator action of certain autacoids. Specifically, these experiments were designed to investigate in the conscious rat 1) the effect of inhibition of endothelium-derived nitric oxide formation by LNMMA on systemic and regional hemodynamics and 2) the interaction between endogenous bradykinin or prostaglandins and nitric oxide. We hypothesized that the contribution of EDRF to the resting...
tone of different vascular beds is variable and that bradykinin or prostaglandins might exert some local effects that are not EDRF dependent.

Methods

Male Wistar rats (Charles River Breeding Laboratories, Inc., Wilmington, Mass.) weighing 300–350 g were used. Cardiac output and regional blood flows were determined by the radioactive microsphere method.\(^1\)\(^9\)\(^,\)\(^2\)\(^0\) We modified this technique by injecting the microspheres into the left atrium to obtain good mixing of microspheres with blood before they reached the coronary artery. Details have been described extensively elsewhere.\(^2\)\(^1\) Briefly, the left atrium was catheterized through a midline thoracotomy with the rat under ether anesthesia and assisted ventilation. For the next 4–6 days, the rat was maintained on Purina rat chow and tap water ad libitum during recovery from the surgery. From the second day after surgery, the catheter was flushed with heparinized (100 units/ml) 5% dextrose solution once every 2 or 3 days to prevent clotting. One day before the experiment, with the rat under light ether anesthesia, the tail and right iliac artery were catheterized with PE-50 tubes that were routed subcutaneously and exteriorized at the back of the neck.

On the day of the experiment, the rat, conscious and unrestrained, was placed in a plastic cage. Blood pressure and heart rate were recorded through a Gould-Statham pressure transducer (Gould Electronics, Cleveland, Ohio) connected to the iliac catheter. Data were recorded on a Gould 3200 paper chart recorder. An infusion/withdrawal pump (model 600-900, Harvard Apparatus, South Natick, Mass.) was connected to the tail catheter for collection of the reference blood sample. A 1-hour stabilization period was observed before initiation of the actual experiment.

Radioactive microspheres (DuPont-New England Nuclear, Boston) 15±1.5 μm in diameter, were labeled with tin-113 (\(^{113}\)Sn) suspended in 2.5% dextran, in 6-cm-long PE-50 tubing with a predetermined concentration of 59 mg/9 ml. Microspheres were mechanically agitated for approximately 5 minutes, and their dispersion by this method was found to be adequate by microscopic examination of one drop of the suspension. The suspension was then withdrawn in 6-cm-long PE-50 tubing with a predetermined volume of 15 μl, which corresponds to approximately 20,000 microspheres. The tubing was sealed and counted to obtain the preinjection dose, mechanically agitated again, and then connected to the left atrium catheter 1 minute before the infusion. The microsphere suspension, together with 300 μl of 5% dextrose for flushing, was infused into the left atrium for 20 seconds. Ten seconds before the microsphere infusion, withdrawal of the arterial reference blood started at a rate of 1.36 ml/min and continued for a total of 75 seconds.

Subsequently, the animals were killed with a 100 mg/kg intravenous dose of pentobarbital sodium (Nembutal, Abbott Laboratories, North Chicago, Ill.). The major organs were removed, weighed, and counted for 1 minute in a gamma well scintillation counter (Auto-Gamma 5650, Packard Instrument Co., Inc., Meriden, Conn.) using an open window (100–1,000) and a sample level allowing constant efficiency zone for the various sample heights. The left atrium catheter and the tubing containing the microspheres were measured for residual radioactivity, which was subtracted from the preinjection dose.

Cardiac output and organ blood flows were determined as follows:

\[
\frac{CO (ml/min)}{radioactivity in blood sample (cpm)}\times radioactivity injected (cpm)
\]

\[
Organ blood flow (ml/min)=\frac{CO (ml/min)}{radioactivity in organ (cpm)}\times radioactivity injected (cpm)
\]

where CO is cardiac output.

Cardiac index (in milliliters per minute per 100 grams) represents cardiac output divided by 100 g of body weight. Stroke volume (in milliliters) was obtained by dividing cardiac output by heart rate. Total peripheral vascular resistance (in millimeters of mercury per milliliter per minute) was estimated by dividing mean arterial pressure by cardiac output. Regional blood flows were expressed as milliliters per minute per gram of organ. Local vascular resistance (in millimeters of mercury per milliliter per minute per gram) was obtained by dividing mean arterial pressure by organ blood flow.

To observe continuously the time course of the changes of blood flow and cardiac output induced by LNMMA injection, we conducted a pilot experiment on two other rats, implanting a single crystal Doppler flow probe (Instrumentation Development Laboratories, Houston, Tex.) around the ascending aorta 10 days before the experiment, as described before.\(^2\)\(^2\) We then measured the blood pressure and the Doppler shift (reflecting cardiac output) continuously by the ultrasonic range-gate 10-kHz pulsed Doppler technique.\(^2\)\(^3\) These data are not included in the statistical evaluation of the results of the five groups of rats described below.

The bradykinin antagonist (BKA) used in this study was the analogue (d-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-d-Phe-Thi-Arg)trifluoroacetic acid, where Thi is β-[2-thienyl]-l-alanine,\(^2\)\(^4\) a B\(_2\) receptor antagonist tested extensively in the past. It was synthesized in our peptide laboratory, and its antagonistic potency was assayed against the vasodepressor effect of exogenous bradykinin in conscious, unrestrained rats as described elsewhere.\(^2\)\(^5\) Infused at the rate of 50 μg/min, it could inhibit the blood pressure–lowering effect of a 250-ng intravenous bolus of bradykinin by 74.5±2.95% \((n=7)\) without stimulating release of catecholamines.\(^2\)\(^1\)\(^,\)\(^2\)\(^5\) BKA, LNMMA, and L-arginine
Figure 1. Line graphs show effect of N\textsuperscript{G}-monomethyl L-arginine (L-NMMA) on mean arterial blood pressure (MAP) and heart rate (HR) in conscious, normotensive rats. Results are mean±SEM. Significance is shown compared with the group's baseline at time 0, before treatment. L-Arg, L-arginine.

Injection of 10 mg/kg LNMMA resulted in an increase in mean arterial pressure accompanied by bradycardia, which reached its peak within 2 minutes and was sustained for approximately 5 minutes (Figures 1 and 2, Table 1). Cardiac output and cardiac index decreased by an average of 30.0% and 35.6% (p<0.01), respectively, and total peripheral vascular resistance increased by 51.6% (p<0.01) compared with the control group (Table 1). Stroke volume did not differ significantly in the two groups.

Experiments were performed on five groups of rats: 1) A control group (n=14) received the vehicle (1 ml/kg of 5% dextrose) followed by a 0.1 ml/min infusion of D5W for 5 minutes, after which the microspheres were injected; 2) an LNMMA group (n=8) was injected with LNMMA (10 mg/kg at 1 ml/kg) followed by the radioactive microspheres; 3) an LNMMA+L-arginine group (n=8) was first injected with L-arginine (100 mg/kg at 0.5 ml/kg) followed immediately by LNMMA (10 mg/kg at 0.5 ml/kg) and by a 0.1 ml/min infusion of D5W for 5 minutes, after which the microspheres were injected; 4) an LNMMA+BKA group (n=8) was infused with BKA (50 \mu g/min at 0.1 ml/min) for 5 minutes and received LNMMA (10 mg/kg at 1 ml/kg) at the beginning of the infusion followed by the microspheres at the fifth minute of the BKA infusion; and 5) an LNMMA+indomethacin group (n=8) was pretreated with indomethacin (10 mg/kg) 1 hour earlier, then received LNMMA, D5W infusion, and microsphere injection as above. The total input and withdrawal of fluids was the same in all groups during the acute experiment.

Results are reported as mean±SEM. Statistical evaluation was performed by analysis of variance on the raw data, followed, when required, by a Student-Newman-Keuls test. Differences were considered to be significant at a value of p<0.05.

Figure 2. Representative recordings show effect of N\textsuperscript{G}-monomethyl L-arginine (L-NMMA) on blood pressure and cardiac output in conscious, normotensive rats. Rat No. 1990110; body weight, 236 g. Upper tracing depicts blood pressure; lower tracing depicts Doppler shift (reflecting cardiac output). Phasic recordings are shown intermittently.
TABLE 1. Effect of \(N^6\)-Monomethyl L-Arginine on Systemic Hemodynamics in Conscious, Normotensive Rats

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control (n=14)</th>
<th>LNMMMA (n=8)</th>
<th>LNMMMA+L-arginine (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats ((n))</td>
<td>14</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Weight ((g))</td>
<td>297.00±4.15</td>
<td>320.88±8.98*</td>
<td>299.25±8.85</td>
</tr>
<tr>
<td>(\Delta)MAP ((\text{mm Hg}))</td>
<td>0.36±0.70</td>
<td>16.25±2.58†</td>
<td>1.88±1.26‡</td>
</tr>
<tr>
<td>(\Delta)HR ((\text{bpm}))</td>
<td>-1.54±1.54</td>
<td>-54.29±16.74*</td>
<td>-20.00±6.17</td>
</tr>
<tr>
<td>CO ((\text{ml/min}))</td>
<td>128.78±7.67</td>
<td>90.14±5.91†</td>
<td>97.52±7.28†</td>
</tr>
<tr>
<td>CI ((\text{ml/min/100 g}))</td>
<td>43.49±2.66</td>
<td>28.03±1.38†</td>
<td>32.50±1.88†</td>
</tr>
<tr>
<td>SV ((\text{ml}))</td>
<td>0.30±0.02</td>
<td>0.27±0.02</td>
<td>0.26±0.02</td>
</tr>
<tr>
<td>TPVR ((\text{mm Hg/ml/min}))</td>
<td>0.93±0.07</td>
<td>1.41±0.09†</td>
<td>1.19±0.10*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Changes in mean arterial pressure \((\Delta\)MAP\) and heart rate \((\Delta\)HR\) are shown at 5 minutes after 5% dextrose in the control group or appropriate drug or drugs in treatment groups. LNMMMA, \(N^6\)-monomethyl L-arginine; bpm, beats per minute; CO, cardiac output; CI, cardiac index; SV, stroke volume; TPVR, total peripheral vascular resistance.

*\(p<0.05\), †\(p<0.01\), treatment vs. control.

\#\(p<0.05\), LNMMMA vs. LNMMMA+L-arginine.

LNMMMA decreased regional blood flows (Figure 3) and increased vascular resistances (Figure 4) in most organs. The changes were significant in the heart, kidney, stomach, large intestine, skin, and adrenals \((p<0.05)\).

**Effects of L-Arginine on the Hemodynamic Action of \(N^6\)-Monomethyl L-Arginine**

Preinjection of L-arginine \((100 \text{ mg/kg})\) prevented the pressor response induced by LNMMMA (Figure 1). It tended to attenuate the changes in heart rate, cardiac output, cardiac index, and total peripheral resistance (Table 1), but these changes were not statistically significant. L-Arginine itself did not affect significantly baseline blood pressure \((\text{from } 109.8±3.7 \text{ to } 110.3±3.6 \text{ mm Hg})\) or heart rate \((\text{from } 405.0±10.5 \text{ to } 397.1±11.9 \text{ beats per minute})\).

On the regional level (Figures 3 and 4), L-arginine prevented the LNMMMA-induced circulatory changes in the large intestine, testes, and adrenals but did not affect those in the heart, kidney, small intestine, stomach, and skin. Regional flows to the brain, liver, and muscle were not significantly affected by either one of these two interventions. In the spleen, whose hemodynamics were unaffected by LNMMMA alone, blood flow significantly increased and vascular resistance decreased with the combination of L-arginine and LNMMMA.

**Effects of \(N^6\)-Monomethyl L-Arginine on Systemic and Regional Hemodynamics in Rats Preinjected With Bradykinin Antagonist**

Infusion of a BKA followed by an injection of LNMMMA resulted in systemic (Table 2) and regional (Tables 3 and 4) hemodynamic changes similar to those observed with LNMMMA alone.

**Effects of \(N^6\)-Monomethyl L-Arginine on Systemic and Regional Hemodynamics in Rats Pretreated With Indomethacin**

In rats pretreated with indomethacin, LNMMMA also produced systemic (Table 2) and regional (Tables 3 and 4) hemodynamic changes in most organs similar to those produced by LNMMMA alone. However, in the cerebral and bronchial circulation, blood flow decreased by an additional 44.24% and 38.33% on average, and local vascular resistance increased by 75.26% and 139.48%, respectively; in the liver, blood flow increased by an additional 257%, and vascular...
resistance decreased by 48.52% compared with values obtained with LNMMA alone (Tables 3 and 4).

Discussion
Several recent studies have demonstrated that the L-arginine analogue LNMMA, which inhibits the formation of nitric oxide by endothelial cells, elicits significant increases in systemic blood pressure, accompanied by bradycardia in the anesthetized rabbit, rat, and guinea pig. In humans, this compound was shown to decrease the basal forearm blood flow by 50%. Endothelium-derived nitric oxide is the final mediator of many vasodilator substances, as mentioned above. However, different vascular trees may display different sensitivity to the action of a given vasoactive substance, as has been shown in the past for angiotensin, bradykinin, vasopressin, and others.

Our results confirmed the anticipated increase in systemic vascular resistance and blood pressure, accompanied by bradycardia, which probably was due to baroreceptor activation. There was also a significant decrease in cardiac output and cardiac index, probably attributable in part to increased afterload and in part to decreased myocardial perfusion, as shown by the markedly diminished coronary blood flow. Because afterload is one of the determinants of coronary flow, its increase would be expected to lead to coronary vasodilation, which is in part EDRF dependent. Thus, inhibition of EDRF formation by LNMMA in the present experiments led to diminished myocardial perfusion and probably impaired contractility. It is possible, of course, that the decreased cardiac output itself contributed to the decline in coronary flow. However, not all regional flows decreased commensurately with the fall in cardiac output. For example, cerebral blood flow decreased by only 17.79%, as opposed to a 50.15% decrease in adrenal blood flow. These findings indicate that changes in fractional output distribution reflect differences in the dependency of local vascular tone on EDRF.

The EDRF precursor L-arginine could overcome the inhibitory effect of LNMMA and thus abolish or attenuate its vasoconstricting action to a variable extent in different vascular beds. Gardiner et al. using Doppler flow probes, also found that the responses to LNMMA in the renal and mesenteric
Table 3. Effect of Combination of Bradykinin Antagonist or Indomethacin and \( \text{N}^{\text{G}} \)-Monomethyl \( \text{L} \)-Arginine on Regional Blood Flow in Conscious, Normotensive Rats

<table>
<thead>
<tr>
<th>Region</th>
<th>LNMMA (n=8)</th>
<th>LNMMA+BKA (n=8)</th>
<th>LNMMA+indomethacin (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>3.00±0.27</td>
<td>3.24±0.27</td>
<td>2.96±0.30</td>
</tr>
<tr>
<td>Bronchial</td>
<td>0.60±0.07</td>
<td>0.47±0.04</td>
<td>0.37±0.09</td>
</tr>
<tr>
<td>Liver</td>
<td>0.07±0.01</td>
<td>0.07±0.02*</td>
<td>0.25±0.06†</td>
</tr>
<tr>
<td>Spleen</td>
<td>2.27±0.32</td>
<td>2.06±0.24</td>
<td>1.87±0.22</td>
</tr>
<tr>
<td>Kidney</td>
<td>4.56±0.25</td>
<td>3.82±0.43</td>
<td>4.06±0.25</td>
</tr>
<tr>
<td>Testis</td>
<td>0.24±0.01</td>
<td>0.22±0.01</td>
<td>0.27±0.02</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.54±0.05</td>
<td>0.59±0.07</td>
<td>0.56±0.05</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1.25±0.07</td>
<td>1.31±0.11</td>
<td>1.43±0.11</td>
</tr>
<tr>
<td>Large intestine</td>
<td>0.92±0.04</td>
<td>0.88±0.05</td>
<td>1.07±0.15</td>
</tr>
<tr>
<td>Brain</td>
<td>1.05±0.08</td>
<td>0.97±0.07*</td>
<td>0.58±0.04†</td>
</tr>
<tr>
<td>Skin</td>
<td>0.12±0.01</td>
<td>0.11±0.01</td>
<td>0.12±0.01</td>
</tr>
<tr>
<td>Muscle</td>
<td>0.11±0.01</td>
<td>0.16±0.02</td>
<td>0.11±0.00</td>
</tr>
<tr>
<td>Adrenal</td>
<td>1.69±0.10</td>
<td>2.18±0.42</td>
<td>1.69±0.10</td>
</tr>
</tbody>
</table>

Values are mean±SEM in milliliters per minute per gram. LNMMA, \( \text{N}^{\text{G}} \)-monomethyl \( \text{L} \)-arginine; BKA, bradykinin antagonist.

*p<0.01, LNMMA+BKA vs. LNMMA+indomethacin group.

†p<0.01, LNMMA vs. LNMMA+BKA or LNMMA+indomethacin group.

vasculatures were totally or almost totally reversed by \( \text{L} \)-arginine, but the conductance in the internal carotid and hindquarters was only partially restored to pretreatment levels. Similar results were obtained in rats treated with \( \text{N}^{\text{G}} \)-nitro-\( \text{L} \)-arginine, another inhibitor of nitric oxide formation. By using the radioactive microsphere method, we could measure changes in the perfusion of tissues that are not measurable by Doppler.

The pattern of regional blood flow redistribution after LNMMA is directionally similar, though not identical, to that of inhibition of endogenous bradykinin, which is one of the endothelium-dependent vasodilators. Indeed, the heart and kidneys had the greatest decreases with either LNMMA or the BKA alone, whereas the brain circulation showed no change with either one. The combination of LNMMA with a BKA in the present study did not induce additional systemic and regional hemodynamic changes compared with those obtained with LNMMA alone. These results further support the notion that the vasoactive effects of endogenous bradykinin are nitric oxide mediated, a finding in agreement with previous reports demonstrating that inhibition of nitric oxide formation by LNMMA can diminish the systemic and regional vasodilator effects of exogenous bradykinin.

Prostacyclin is one of the endothelium-independent vasodilators, as shown by the failure of

Table 4. Effect of Combination of Bradykinin Antagonist or Indomethacin and \( \text{N}^{\text{G}} \)-Monomethyl \( \text{L} \)-Arginine on Regional Vascular Resistance in Conscious, Normotensive Rats

<table>
<thead>
<tr>
<th>Region</th>
<th>LNMMA (n=8)</th>
<th>LNMMA+BKA (n=8)</th>
<th>LNMMA+indomethacin (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>43.01±3.86</td>
<td>41.23±4.66</td>
<td>45.27±3.89</td>
</tr>
<tr>
<td>Bronchial</td>
<td>225.61±27.65</td>
<td>282.68±28.17*</td>
<td>540.30±114.73†</td>
</tr>
<tr>
<td>Liver</td>
<td>2,019.92±233.82</td>
<td>2,809.97±552.31*</td>
<td>1,076.90±423.54</td>
</tr>
<tr>
<td>Spleen</td>
<td>61.47±7.51</td>
<td>71.28±14.07</td>
<td>71.93±5.50</td>
</tr>
<tr>
<td>Kidney</td>
<td>27.80±1.83</td>
<td>34.21±6.73</td>
<td>33.15±1.91</td>
</tr>
<tr>
<td>Testis</td>
<td>535.13±37.36</td>
<td>565.88±76.69</td>
<td>501.85±43.95</td>
</tr>
<tr>
<td>Stomach</td>
<td>244.65±27.00</td>
<td>299.66±25.57</td>
<td>237.37±18.90</td>
</tr>
<tr>
<td>Small intestine</td>
<td>101.34±6.30</td>
<td>99.06±7.64</td>
<td>92.10±8.18</td>
</tr>
<tr>
<td>Large intestine</td>
<td>135.61±6.12</td>
<td>146.39±11.74</td>
<td>132.52±15.92</td>
</tr>
<tr>
<td>Brain</td>
<td>124.93±12.43</td>
<td>135.32±13.65*</td>
<td>218.95±8.06*</td>
</tr>
<tr>
<td>Skin</td>
<td>1,063.97±110.36</td>
<td>1,194.21±136.70</td>
<td>1,166.79±123.37</td>
</tr>
<tr>
<td>Muscle</td>
<td>1,258.03±132.53</td>
<td>868.26±103.25</td>
<td>1,240.27±126.12</td>
</tr>
<tr>
<td>Adrenal</td>
<td>76.52±3.71</td>
<td>93.69±54.45</td>
<td>101.46±23.87</td>
</tr>
</tbody>
</table>

Values are mean±SEM in millimeters of mercury per milliliter per minute per gram. LNMMA, \( \text{N}^{\text{G}} \)-monomethyl \( \text{L} \)-arginine; BKA, bradykinin antagonist.

*p<0.05, LNMMA+BKA vs. LNMMA+indomethacin group.

†p<0.05, LNMMA vs. LNMMA+BKA or LNMMA+indomethacin group.
LNMMMA to inhibit the vasodepressor responses to prostaglandin. The hemodynamic effects of inhibition of prostaglandin synthesis by cyclooxygenase inhibition differ from those induced by LNMMMA mostly in the cerebral blood flow, which decreased by an average of 47.57% with indomethacin alone but did not significantly change with LNMMMA. Combination of both in the present study resulted in a 54.16% reduction ($p<0.01$), apparently attributable entirely to indomethacin and suggesting that prostaglandins are the predominant cerebral vasodilator.

In conclusion, in conscious, normotensive rats, inhibition of nitric oxide formation by LNMMMA led to an increase in systemic blood pressure accompanied by bradycardia, a decrease in cardiac output, and an increase in total peripheral vascular resistance. Regional blood flow decreased and vascular resistance rose to variable extents in most organs except in the bronchial circulation. These responses could be prevented or attenuated by pretreatment with the EDRF precursor L-arginine. The results suggest that endothelium-derived nitric oxide is continuously released in the local arterial bed of different organs, where it has a major role in determining resting tone and regulating blood flow. Endothelium-derived nitric oxide was shown to mediate the vasodilator effect of bradykinin in most vascular beds; on the contrary, that of prostaglandins was not always EDRF dependent, a fact most notable in the cerebral circulation.

References


Key Words: endothelium • nitric oxide • bradykinin • indomethacin • blood flow • arginine vasopressin • microspheres
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