Cardiac Afferents Attenuate Renal Sympathetic Baroreceptor Reflexes During Acute Hypertension

Patricia K. Dorward, Leonard B. Bell, and Carl D. Rudd

We have studied the effect of acute hypertensive episodes on the renal sympathetic baroreceptor reflex in conscious rabbits and the role played by cardiac afferents and endogenous opiate mechanisms. Renal sympathetic nerve activity was recorded during brief perivascular balloon-induced ramp changes in mean arterial pressure before and during 40-minute elevations in resting pressure. Methoxamine infusion was adjusted to increase pressure by +30 and +45 mm Hg in the presence of autonomic blockade of the heart with atenolol and methscopolamine. Experiments were repeated in other rabbits after blocking cardiac afferents with 5% intrapericardial procaine or during intravenous naloxone (4–6 mg/kg, then 0.12 mg/kg/min). We found a progressively severe attenuation of the renal sympathetic baroreceptor reflex during increasing elevations in resting pressure. The upper plateau and range of the reflex curve were both reduced by one third and two thirds during moderate and severe hypertension, respectively. The average gain fell by 64% and 87%, and the range-independent gain and hypotensive reversal response were also reduced. There was no resetting of the reflex to higher pressures as would be expected. One third of the reflex inhibition was prevented by blocking cardiac afferents; none of it was affected by intravenous naloxone, which had previously been shown to reverse the renal baroreceptor reflex depression elicited by hemorrhagic hypotension. Factors possibly responsible for the remaining two thirds of the hypertension-induced sympathoinhibition are suggested to be either central depression of sympathetic tone after elevation of arterial baroreceptor discharge during the hypertensive episode or additional inhibitory afferent input arising from the pulmonary circulation. (Hypertension 1990;16:131–139)
hypertensive episodes and to influence the baroreceptor reflex control of renal nerve activity.

During sustained periods of hypotension elicited by severe hemorrhage in conscious rabbits, cardiac receptor inhibition is again pronounced and involves central nervous pathways containing opiate-sensitive synapses that are blocked with intravenous or intracisternal naloxone.14,15 Therefore, it was of interest to see if similar pathways were involved when cardiac receptors were activated by increased chamber volume during hypertensive episodes.

Our aims in these experiments were 1) to study the baroreceptor reflex control of renal SNA during hypertensive episodes of increasing severity, 2) to determine if any observed effects were dependent on alterations in cardiac afferent input, and 3) to see if the afferents involved could be characterized by the possession of an opioid link in their central nervous pathways. Two levels of methoxamine-induced hypertension (+30 and +45 mm Hg for 40 minutes) were studied sequentially in three groups of rabbits: 1) control rabbits, 2) rabbits treated with intrapericardial procaine, and 3) rabbits receiving intravenous naloxone infusion.

Methods

Surgical Procedures and Recordings

We used 20 crossbred rabbits in which experiments were conducted in accordance with the statement on animal experimentation by the National Health and Medical Research Council of Australia. Three preliminary operations were performed under halothane anesthesia after induction with alfathesin (alpha-Metyramine) (concentration, 1.5 mg/kg i.v. bolus followed by 1.8 mg/kg/min infusion). A fourth group of rabbits was studied as a time control. Rabbits received pericardial saline but no heart block or methoxamine infusion, and repeated baroreceptor reflex assessments were made at time intervals that matched those used in the other three groups.

Initially, the renal sympathetic baroreceptor reflex was assessed from the average of triplicate estimates to give a calibration curve that was used to normalize all other curves (see below). We have routinely found that responses to the first two or three pairs of balloon inflations of the day were larger than those elicited by subsequent inflation pairs (P.K. Dorward, unpublished observations), so these were not included in the calibration curve. Next, heart block was administered, and the treatment regimen was started. After half an hour, the baroreceptor reflex was determined again in triplicate to give the control curve for the treatment regimen at normal blood pressure. Finally, pressure was elevated by infusing methoxamine hydrochloride (concentration, 3 mg/kg/ml) at rates between 2 and 8 ml/hr, which were adjusted to produce successive pressure increases of approximately 30 mm Hg (moderate hypertension) and then 40–45 mm Hg (severe hypertension). Twenty minutes after each pressure level had been achieved, the baroreceptor reflex was assessed in triplicate, taking about 15–20 minutes.

Mean Arterial Pressure–Renal Sympathetic Nerve Activity Baroreceptor Reflex Relation

The renal sympathetic baroreceptor reflex was derived from slow ramp falls and rises in intravascular pressure obtained by inflating alternately the caval and aortic balloon cuffs. Cuff inflation produces
complex but directionally similar changes in various intravascular pressures, and we have used MAP as an index of these changes, as previously described. A sigmoidal logistic function was fitted to the MAP-renal SNA data points by an iterative least-squares method, using a general nonlinear regression equation:

\[ \text{Renal SNA} = P_1 + P_2 / \{1 + \exp[P_3(MAP - P_4)]\} \]

where \( P_1 \) is the lower plateau, \( P_2 \) is the range between the upper and lower plateaus, \( P_3 \) is a range-independent measure of slope or normalized gain, and \( P_4 \) is MAP at half the renal SNA range (BP50). The average range-dependent gain, which was estimated between the inflection points of the curve, was \(-P_2 \times P_3/4.56\); the upper plateau equaled \( P_1 + P_2 \). The renal SNA value at minimum MAP (the hypotensive value) and the corresponding value at maximum MAP (the hypertensive value) were also recorded, and from these we derived the hypotensive reversal (upper plateau minus hypotensive value) and the hypertensive reversal (hypertensive value minus lower plateau) as previously described.

Due to the wide variation we routinely found in the microvolt levels of nerve activity recorded from different rabbits, we normalized the curves in each rabbit by expressing renal SNA in terms of the upper plateau level of the initial calibration curve, which was taken to equal 100 normalized units.

**Statistical Analysis**

Differences in resting values and baroreceptor reflex curve parameters between triplicate estimates of the calibration curves, the control curves at normal blood pressure during administration of either saline, procaine, or naloxone, and the subsequent curves derived during moderate hypertension and then during severe hypertension were assessed by a split plot three-way analysis of variance. For each group of rabbits, the residual sum of squares was calculated by subtracting the between-rabbit sum of squares and within-rabbit sum of squares from the total sum of squares. A total residual mean square was then calculated for the three groups. In each group, the within-rabbit sum of squares was divided into-betweentreatment sum of squares and between-replicate sum of squares within treatments. The between-treatment sum of squares was partitioned into separate degrees of freedom, and the \( F \) ratio for each partition was calculated using the total residual mean square. The significance of three orthogonal comparisons was assessed including the difference between the control curves and the average of the two episodes of hypertension (partition coefficients for comparison: \( 0,2,-1,-1 \)) and the difference between moderate and severe hypertension (\( 0,0,1,-1 \)). An additional nonorthogonal comparison between calibration and control curves during the three drug regimens (\( 1,-1,0,0 \)) was also made. By use of the Bonferroni procedure, differences were classified as significant if \( p<0.0375 \).

**Results**

**Effect of Hypertensive Episodes on the Renal Sympathetic Baroreceptor Reflex**

Initially, the reproducibility of the renal sympathetic baroreceptor reflex was assessed over a 2-hour period at normal blood pressures (Figure 1). There were no differences between triplicate estimates of the reflex in each time period, and the slight attenuation of the reflex range during the third and fourth period was not statistically significant. Elevations in resting blood pressure were produced sequentially, rather than in a randomized time order, because preliminary experiments showed that triplicate estimates of the baroreceptor reflex were no longer reproducible after hypertensive episodes of this magnitude and that both resting pressure and renal SNA remained depressed, as reported by others. Moderate (+30±1 mm Hg elevation) and severe (+44±1 mm Hg elevation) hypertension were sequentially induced for 35–40 minutes each, and baroreceptor reflex measurements were started 20 minutes after the elevations in pressure.

In the control group of rabbits treated with intrapericardial saline, sequential rises in resting blood pressure produced a progressive reduction of resting renal SNA and depression of the renal sympathetic baroreceptor reflex (Figure 2 and Table 1). Resting renal SNA was indistinguishable from the minimum lower plateau level elicited by balloon-induced pressure rises in four of the five rabbits during moderate hypertension and in all rabbits during severe hypertension. There was a substantial inhibition of the maximum upper plateau level of SNA elicited by transiently lowering MAP with the caval balloon cuff. During moderate and severe hypertension, the upper plateau was reduced to 64.2±7.2 and 31.3±7.2 nor-
TABLE 1. Resting Values and Parameters Describing Average Mean Arterial Pressure–Renal Sympathetic Nerve Activity Curves Derived Before and After Sequential Hypertensive Episodes of Increasing Severity in Five Rabbits Treated With Intrapericardial Saline in the Presence of Different Heart Block With Methscopolamine and Atenolol

<table>
<thead>
<tr>
<th>Saline</th>
<th>Cal</th>
<th>Control</th>
<th>+30 mm Hg</th>
<th>+44 mm Hg</th>
<th>SEM</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotensive value (n.u.)</td>
<td>18.2</td>
<td>18.9</td>
<td>41.5</td>
<td>21.3</td>
<td>±3.4</td>
<td>0.0</td>
<td>1.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Upper plateau (n.u.)</td>
<td>100.0</td>
<td>98.2</td>
<td>64.2</td>
<td>31.3</td>
<td>±7.2</td>
<td>0.6</td>
<td>20.9*</td>
<td>6.7*</td>
</tr>
<tr>
<td>Resting renal SNA (n.u.)</td>
<td>33.3</td>
<td>30.2</td>
<td>8.1</td>
<td>4.4</td>
<td>±2.3</td>
<td>0.7</td>
<td>55.1*</td>
<td>1.0</td>
</tr>
<tr>
<td>Lower plateau (n.u.)</td>
<td>8.3</td>
<td>5.6</td>
<td>3.5</td>
<td>3.2</td>
<td>±1.0</td>
<td>1.8</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertensive value (n.u.)</td>
<td>14.1</td>
<td>12.5</td>
<td>6.5</td>
<td>6.7</td>
<td>±1.3</td>
<td>0.3</td>
<td>4.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Renal SNA range (n.u.)</td>
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<td>92.6</td>
<td>60.7</td>
<td>28.1</td>
<td>±7.0</td>
<td>0.1</td>
<td>19.3*</td>
<td>6.5*</td>
</tr>
<tr>
<td>Average gain (n.u./mm Hg)</td>
<td>-5.1</td>
<td>-6.9</td>
<td>-2.5</td>
<td>-0.9</td>
<td>±0.6</td>
<td>4.2</td>
<td>53.8*</td>
<td>4.0</td>
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<tr>
<td>BP&lt;sub&gt;50&lt;/sub&gt; (mm Hg)</td>
<td>86.1</td>
<td>83.7</td>
<td>87.4</td>
<td>89.0</td>
<td>±2.8</td>
<td>0.5</td>
<td>2.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Resting MAP (mm Hg)</td>
<td>90.5</td>
<td>87.5</td>
<td>117.0</td>
<td>131.5</td>
<td>±1.0</td>
<td>4.0</td>
<td>793*</td>
<td>93.4*</td>
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<tr>
<td>Hypotensive reversal (n.u.)</td>
<td>81.8</td>
<td>79.3</td>
<td>22.7</td>
<td>10.0</td>
<td>±6.5</td>
<td>0.0</td>
<td>74.9*</td>
<td>2.8</td>
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<tr>
<td>Hypertensive reversal (n.u.)</td>
<td>5.8</td>
<td>6.9</td>
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<td>3.5</td>
<td>±1.2</td>
<td>0.4</td>
<td>2.1</td>
<td>0.0</td>
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<tr>
<td>Range-independent gain (P&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>0.26</td>
<td>0.31</td>
<td>0.19</td>
<td>0.17</td>
<td>±0.02</td>
<td>3.1</td>
<td>20.9*</td>
<td>0.5</td>
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Curves were derived during an initial calibration period (Cal), after instilling pericardial saline (Control), and after blood pressure (BP) elevations of +30 mm Hg and +44 mm Hg. SEM is based on analysis of variance. 1, Comparison of calibration and control curves; 2, comparison of control curve with average of two levels of hypertension; 3, comparison of moderate and severe hypertension; n.u., normalized units; SNA, sympathetic nerve activity; BP<sub>50</sub>, mean arterial pressure (MAP) at half the renal SNA range.

*p<0.0375 (see Methods).
upper plateau of the baroreceptor reflex was reduced to 98.6±9.2 and 72.3±9.2 normalized units, respectively, from the elevated value (128.5±9.2 normalized units) elicited by procaine treatment. Similar reductions of 24% and 45% were found in the reflex range. The average baroreceptor reflex gain fell by 39% and 59% during the two levels of hypertension, and there was no longer a significant reduction in normalized gain.

To compare the relative effects of hypertensive episodes in the presence and absence of cardiac receptor input, curves derived during procaine treatment were renormalized so that the upper plateau value of the prehypertension control curve equaled 100%. Upper plateau values during moderate and severe hypertension were 76.7±7.1% and 56.3±7.1% compared with values of 64.2±7.2 and 31.3±7.2 normalized units during saline treatment. During severe hypertension the difference in upper plateaus was no longer a significant reduction in normalized gain.

The effects of intravenous naloxone on the renal sympathetic baroreceptor reflex resembled those of intrapericardial procaine, as previously reported.14

### TABLE 2. Resting Values and Parameters Describing Average Mean Arterial Pressure–Renal Sympathetic Nerve Activity Curves Derived Before and After Sequential Hypertensive Episodes of Increasing Severity in Five Rabbits Treated With Intrapericardial Procaine in the Presence of Efferent Heart Block With Methscopolamine and Atenolol

<table>
<thead>
<tr>
<th>Procaine</th>
<th>Cal BP elevation</th>
<th>SEM</th>
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<th>2</th>
<th>3</th>
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<tbody>
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<td>Hypotensive value (n.u.)</td>
<td>55.4</td>
<td>99.9</td>
<td>83.4</td>
<td>56.4</td>
<td>±8.6</td>
</tr>
<tr>
<td>Upper plateau (n.u.)</td>
<td>100.0</td>
<td>128.5</td>
<td>98.6</td>
<td>72.3</td>
<td>±9.2</td>
</tr>
<tr>
<td>Resting renal SNA (n.u.)</td>
<td>32.3</td>
<td>42.1</td>
<td>12.4</td>
<td>7.6</td>
<td>±2.9</td>
</tr>
<tr>
<td>Lower plateau (n.u.)</td>
<td>6.5</td>
<td>8.1</td>
<td>6.9</td>
<td>5.6</td>
<td>±1.6</td>
</tr>
<tr>
<td>Hypertensive value (n.u.)</td>
<td>20.0</td>
<td>19.2</td>
<td>11.4</td>
<td>12.4</td>
<td>±3.2</td>
</tr>
<tr>
<td>Renal SNA range (n.u.)</td>
<td>93.5</td>
<td>120.4</td>
<td>91.7</td>
<td>66.7</td>
<td>±9.5</td>
</tr>
<tr>
<td>Average gain (n.u/mm Hg)</td>
<td>−4.9</td>
<td>−5.1</td>
<td>−3.1</td>
<td>−2.1</td>
<td>±0.6</td>
</tr>
<tr>
<td>BP&lt;sub&gt;50&lt;/sub&gt; (mm Hg)</td>
<td>82.7</td>
<td>82.8</td>
<td>83.5</td>
<td>89.7</td>
<td>±2.5</td>
</tr>
<tr>
<td>Resting MAP (mm Hg)</td>
<td>87.9</td>
<td>87.8</td>
<td>117.2</td>
<td>132.2</td>
<td>±1.2</td>
</tr>
<tr>
<td>Hypotensive reversal (n.u.)</td>
<td>44.6</td>
<td>28.6</td>
<td>15.2</td>
<td>15.9</td>
<td>±5.2</td>
</tr>
<tr>
<td>Hypertensive reversal (n.u.)</td>
<td>13.5</td>
<td>11.1</td>
<td>4.5</td>
<td>6.8</td>
<td>±2.9</td>
</tr>
<tr>
<td>Range-independent gain (P&lt;sub&gt;50&lt;/sub&gt;)</td>
<td>0.24</td>
<td>0.20</td>
<td>0.16</td>
<td>0.16</td>
<td>±0.02</td>
</tr>
</tbody>
</table>

Curves were derived during an initial calibration period (Cal), after instilling pericardial procaine (Control), and after blood pressure (BP) elevations of +29 mm Hg and +44 mm Hg. SEM is based on analysis of variance. 1, Comparison of calibration and procaine curves; 2, comparison of the control curve (procaine) with the average of two levels of hypertension; 3, comparison of moderate and severe hypertension; n.u., normalized units; SNA, sympathetic nerve activity; BP<sub>50</sub>, mean arterial pressure (MAP) at half the renal SNA range. *p<0.00375 (see Methods).
The reflex was augmented with elevations in the upper plateau, range, hypertensive value, and resting renal SNA and a reduction in the hypotensive reversal response (Figure 4 and Table 3). However, in contrast to procaine treatment, naloxone did not diminish the inhibition of the baroreceptor reflex produced by moderate and severe hypertension (+29±2 and +41±2 mm Hg, respectively). The percent reductions in the upper plateau, from the elevated value elicited by naloxone infusion, were larger than those seen in rabbits treated with intrapericardial saline. However, the difference between the two treatments was not statistically significant. Large reductions were also seen in the reflex range and gain, and the hypotensive reversal response was virtually abolished (Figure 4 and Table 3). Yet again, we found no change in the BP50 during hypertension; this finding indicated an absence of reflex resetting, as seen in control and procaine-treated rabbits.

**TABLE 3. Resting Values and Parameters Describing Average Mean Arterial Pressure-Renal Sympathetic Nerve Activity Curves Derived Before and After Sequential Hypertensive Episodes of Increasing Severity in Five Rabbits Treated With Intravenous Naloxone in the Presence of Efferent Heart Block With Methscopolamine and Atenolol**

<table>
<thead>
<tr>
<th></th>
<th>Naloxone</th>
<th>BP elevation</th>
<th>SEM</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotensive value (n.u.)</td>
<td>24.6</td>
<td>+29 mm Hg</td>
<td>+41 mm Hg</td>
<td>±14.0</td>
<td>14.6*</td>
<td>7.9*</td>
</tr>
<tr>
<td>Upper plateau (n.u.)</td>
<td>100.0</td>
<td>125.7</td>
<td>63.9</td>
<td>±12.1</td>
<td>4.6*</td>
<td>67.3*</td>
</tr>
<tr>
<td>Resting renal SNA (n.u.)</td>
<td>25.5</td>
<td>33.6</td>
<td>9.7</td>
<td>±1.1</td>
<td>5.7*</td>
<td>65.5*</td>
</tr>
<tr>
<td>Lower plateau (n.u.)</td>
<td>9.0</td>
<td>14.0</td>
<td>7.6</td>
<td>±1.8</td>
<td>7.2*</td>
<td>14.0*</td>
</tr>
<tr>
<td>Hypertensive value (n.u.)</td>
<td>12.0</td>
<td>19.0</td>
<td>13.0</td>
<td>±1.9</td>
<td>5.5*</td>
<td>4.6*</td>
</tr>
<tr>
<td>Renal SNA range (n.u.)</td>
<td>91.0</td>
<td>111.7</td>
<td>56.3</td>
<td>±11.8</td>
<td>5.5*</td>
<td>13.0*</td>
</tr>
<tr>
<td>Average gain (n.u./mm Hg)</td>
<td>−6.0</td>
<td>−6.9</td>
<td>−2.8</td>
<td>±0.7</td>
<td>1.5</td>
<td>67.4*</td>
</tr>
<tr>
<td>BP50 (mm Hg)</td>
<td>81.5</td>
<td>75.0</td>
<td>74.3</td>
<td>±2.6</td>
<td>3.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Resting MAP (mm Hg)</td>
<td>87.2</td>
<td>81.9</td>
<td>110.6</td>
<td>±1.5</td>
<td>12.2*</td>
<td>710*</td>
</tr>
<tr>
<td>Hypotensive reversal (n.u.)</td>
<td>75.2</td>
<td>58.6</td>
<td>5.3</td>
<td>±6.8</td>
<td>5.3*</td>
<td>17.4*</td>
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<tr>
<td>Hypertensive reversal (n.u.)</td>
<td>3.0</td>
<td>5.0</td>
<td>5.4</td>
<td>±2.3</td>
<td>0.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Range-independent gain (P2)</td>
<td>0.30</td>
<td>0.20</td>
<td>0.18</td>
<td>±0.04</td>
<td>0.0</td>
<td>12.6*</td>
</tr>
</tbody>
</table>

Curves were derived during an initial calibration period (Cal), after starting naloxone infusion (Control), and after blood pressure (BP) elevations of +29 mm Hg and +41 mm Hg. SEM is based on analysis of variance. 1, Comparison of calibration and naloxone curves; 2, comparison of the control curve (naloxone) with the average of the two levels of hypertension; 3, comparison of moderate and severe hypertension; n.u., normalized units; SNA, sympathetic nerve activity; BP50, mean arterial pressure (MAP) at half the renal SNA range. *p<0.0375 (see Methods).

**FIGURE 4.** Graphs showing relation between renal sympathetic nerve activity and mean arterial pressure in five rabbits subjected sequentially to moderate hypertensive episodes (+29±2 mm Hg elevation, left panel) and severe hypertensive episodes (+41±2 mm Hg elevation, right panel) during treatment with intravenous naloxone. In each panel, the dotted line gives the initial calibration curve, and the solid line shows the effect of naloxone during the prehypertension control period. The broken line shows the effect of subsequent hypertension, and the shaded area estimates hypertension-induced inhibition in the presence of naloxone. Triangles and large and small circles represent resting values.

**Discussion**

We have found a marked depression of the renal sympathetic baroreceptor reflex during hypertensive episodes of 40 minutes, which were induced by methoxamine infusion during blockade of cardiac efferent nerves. Moderate and severe elevations in arterial pressure of 30 and 45 mm Hg, respectively, produced progressive attenuation of most baroreceptor reflex curve parameters. Transient balloon-induced reductions in pressure and arterial baroreceptor input were no longer able to evoke the usual rise in renal SNA, with the upper plateau and range of the reflex curve both being reduced by one third and two thirds during moderate and severe hypertension, respectively. This occurrence resulted in pronounced reductions in the gain of the baroreceptor reflex so that its buffering capacity became severely limited. In addition, the pressure threshold and
pressure range over which the reflex operated (midpoint estimated by the BP<sub>50</sub>) did not reset to higher pressures, as would be expected from the arterial baroreceptor resetting that occurs during sustained increases in resting pressure of this magnitude.1-5

These results contrast with the situation found during mild phenylephrine-induced hypertension, when the range of the renal sympathetic baroreceptor reflex was augmented and resetting of reflexes to higher pressures was observed.6

We examined whether cardiac afferent input and endogenous opiate systems contribute to the baroreceptor reflex inhibition that occurs during acute hypertension by studying rabbits treated with intrapericardial procaine and intravenous naloxone. Previous studies<sup>6,17,23</sup> have shown that the dose of procaine used is effective in blocking both efferent and afferent cardiac nerve activity. The dose of naloxone selected in these experiments was the same as that previously used to prevent the abrupt fall in peripheral resistance, resting renal SNA, and the inhibition of the renal sympathetic baroreceptor reflex elicited by hemorrhage in conscious rabbits.13,24 In the present experiments, both treatments augmented the baroreceptor reflex at normal blood pressures, with increases in reflex range similar to those previously reported.6,14 As before, the hypotensive reversal response was significantly reduced, although the magnitude of the reduction with both treatments was less than that found in the earlier studies. Complete abolition of the hypotensive reversal response has been reported by combining sinoaortic denervation with removal of cardiac receptor input, but not by blocking cardiac afferents alone or with the dose of naloxone used in these experiments.6,14 It is possible that the noncardiac afferent and nonopioid-dependent components of the hypotensive reversal response are larger in this study, although the reason for this is unclear. Therefore, we considered that adequate levels of cardiac afferent blockade had been achieved, both peripherally at the pericardial afferent fibers and centrally at the opiate synapses involved in the sympathoinhibition observed during caval cuff inflation or hemorrhage in this species.14,15

The influences of arterial, cardiac, and other baroreceptors on reflex responses in the renal nerve during brief balloon-induced changes in intravascular pressure have previously been studied, and cardiac receptors were found to contribute to the inhibition of SNA at all pressure levels.6 Their contribution is small during small pressure changes but becomes substantial during large falls and rises in pressure. In this study, we have found that cardiac afferents also contributed to the depression of the renal sympathetic baroreceptor reflex during more sustained hypertensive episodes, lasting for over an hour. They are responsible for about one third of the reduction in the upper plateau, renal SNA range, and average gain of the reflex and for the increase in the pressure range over which the reflex operates. We presume that there is a sustained increase in cardiac afferent activity due to an increase in resting chamber volume during acute hypertension and that the variable level of cardiac receptor stimulation elicited by balloon inflation is superimposed on this.

Superficially, the hypertension-induced inhibition of the renal sympathetic baroreceptor reflex that we have found in these experiments resembles the baroreceptor reflex inhibition previously described when both blood pressure and blood volume are reduced by severe hemorrhage.14 Afferent input from the heart is involved during both cases, although in hemorrhage it is responsible for a greater proportion of the reflex inhibition than in acute hypertension. Moreover, there is a major difference in the involvement of endogenous opiate mechanisms at low and high resting pressures. During hemorrhage, all of the baroreceptor reflex inhibition was prevented by infusing intravenous naloxone; this occurrence suggests that the cardiac receptors involved possess an opiate synapse on their reflex pathways to the renal nerve, most probably located in the central nervous system. These conclusions have recently been supported by comparing the effects of intracisternal naloxone and cardiac nerve blockade during simulated hemorrhage in conscious rabbits.15 Interestingly, there are species differences in the pharmacology of the central pathways activated by cardiac afferents during hemorrhage. In rats, the inhibition of renal SNA by vagal cardiac afferents during hemorrhage is unaffected by naloxone and appears to be mediated by serotonergic mechanisms.24-26 In contrast to the dominant influences of opiate mechanisms during hemorrhage-induced hypotension in rabbits, they are not involved in the inhibition of baroreceptor reflex responses elicited by drug-induced hypertension. This finding suggests that different groups of cardiac receptors are responsible for the depression of the renal sympathetic baroreceptor reflex at high and low blood pressures and that their afferent fibers project to interneuron pools in the central nervous system with different pharmacological characteristics.

A considerable proportion of the baroreceptor reflex inhibition during acute hypertensive episodes cannot be attributed to cardiac afferents. Nor are they the factor responsible for offsetting the effects of arterial baroreceptor resetting. The thresholds of arterial baroreceptors are rapidly reset during drug-induced pressure changes of this magnitude and duration, and they continue to operate over a higher pressure range with no reduction in gain.3,4 Therefore, a change in arterial baroreceptor gain cannot explain the reduction in baroreceptor reflex gain seen in these experiments. However, sustained periods of elevated arterial baroreceptor input produced either by electrical stimulation of the aortic nerve or by phenylephrine-induced pressure elevation cause a sustained sympathoinhibition after the return of pressure to control levels.8,9 Our experiments reveal the presence of a similar sympathoinhibition during the period of pressure elevation, and it is possible
that sustained arterial baroreceptor discharge can cause a suppression of the central cell groups involved in the generation of renal sympathetic tone. The extent of this inhibition is revealed when arterial baroreceptor input is transiently reduced by balloon-induced pressure falls. In our experiments, however, such an effect of prolonged baroreceptor activation is not occurring through opiate systems in contrast to the depressor response that is induced by prolonged stimulation of the sciatic nerve in rats. It is unlikely that the effects we see are due to a central action of methoxamine because the central administration of phenylephrine, another \( \alpha \)-adrenergic receptor agonist, augmented the gain of the renal sympathetic baroreceptor reflex, in contrast to our findings.

We have previously found evidence for nonarterial, noncardiac baroreceptor inhibitory influences on renal SNA during balloon-induced pressure changes. Tonic inhibition of the vasomotor center has been reported to arise from vagal afferents supplying the pulmonary vessels. It is possible that afferent input from baroreceptors in the pulmonary circulation is also increased during drug-induced hypertension and contributes to the resulting baroreceptor reflex inhibition and lack of reflex resetting. Our results highlight the compound nature of “baroreceptor reflexes” in intact, conscious animals and the magnitude of the reflex drive from nonarterial baroreceptors that can be engaged during large circulatory disturbances.

The inhibition of the renal sympathetic baroreceptor reflex during acute hypertensive episodes in conscious rabbits is predominantly due to an inhibition of the vasoonstrictor response to unloading the arterial baroreceptors by transiently reducing pressure. Thus, it resembles the reduction in the Valsalva vasoconstrictor reflex response that occurs in chronic human hypertension. Because vascular hypertrophy in hypertension causes an amplification of resistance changes during vasoconstriction, it appeared that the neural component of the Valsalva constrictor response was substantially reduced. Although the thresholds of atrial baroreceptors have been shown to reset to higher pressures in spontaneously hypertensive rats, changes in the characteristics of ventricular or pulmonary baroreceptors have not been studied. In conjunction with earlier studies in clinical hypertension, our results suggest that reflex drive from cardiopulmonary baroreceptors may well remain augmented in chronic hypertension and contribute to a suppression of vasoconstrictor reflexes.

In conclusion, we have demonstrated a substantial depression of the renal sympathetic baroreceptor reflex during methoxamine-induced hypertension in conscious rabbits, which is partly mediated through inhibitory afferent input from cardiac receptors. A considerable component of the baroreceptor reflex depression was not accounted for. The central connections of the cardiac receptors engaged during acute hypertension, and of other afferent mechanisms that may also be involved, do not contain opiate synapses in contrast to those excited by hemorrhagic hypotension.

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References


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