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Somatosensory influences on renal sympathetic nerve activity in anesthetized Wistar and hypertensive rats

TAO ZHANG AND EDWARD J. JOHNS
Department of Physiology, The Medical School, Birmingham B15 2TT, United Kingdom

Zhang, Tao, and Edward J. Johns. Somatosensory influences on renal sympathetic nerve activity in anesthetized Wistar and hypertensive rats. Am J Physiol 272 (Regulatory Integrative Comp. Physiol. 41): R982-R990, 1997.—This study compared the cardiovascular and renal nerve activity responses to somatosensory stimulation with capsaicin in normotensive and hypertensive rats. The importance of the cardiopulmonary receptors in these two states was examined with the use of phenylbiguanide (PBG) infusion. Subcutaneous capsaicin increased blood pressure (BP), heart rate (HR), and renal nerve activity (RNA) 6–35% ($P < 0.01$), and total power (TP) and %power at HR (%PHR) rose two- to threefold ($P < 0.001$). PBG reduced basal RNA, TP, and %PHR (20–70%, $P < 0.05$). PBG did not change the cardiovascular, but attenuated the TP and %PHR increases due to capsaicin ($P < 0.001–0.01$). PBG given to vagotomized normotensive rats normalized the cardiovascular and RNA responses to capsaicin. In hypertensive rats, capsaicin increased BP, HR, RNA (10–20%), TP, and %PHR (50–70%, $P < 0.001$). PBG infusion into hypertensive rats decreased RNA (20%, $P < 0.01$) and the capsaicin-dependent rise in RNA was smaller ($P < 0.05$). TP and %PHR were unchanged, except in vagotomized hypertensive rats given PBG, in which these responses were minimally affected. Somatosensory modulation of RNA power spectra was suppressed by the cardiopulmonary receptors in normotensive rats, but in hypertensive rats their impact was much smaller.

capsaicin; phenylbiguanide; cardiopulmonary receptors

There is accumulating evidence that in many forms of hypertensive disease the sympathetic nervous system contributes to the maintenance of the chronically elevated blood pressure (20). The sympathetic neural control of the kidney is particularly important in this regard because of the innervation of the renin-containing cells, the tubules, and vasculature of the kidney (1), which can directly determine the level of activity of the renin-angiotensin system, sodium retention, and renal vascular resistance, all of which can have a major impact on cardiovascular homeostasis (16). A role for exaggerated renal nerve activity at a functional level comes from a number of studies. For example, Wyss et al. (27) showed that the development of hypertension in the growing spontaneously hypertensive rat (SHR) was delayed by bilateral renal denervation. Our own studies demonstrated exaggerated renal sympathetic drive to renal release and expression of the renin gene from the young to adult state (19), whereas pharmacological activation of central nervous system 5-hydroxytryptamine (5-HT)$_1$ receptors with flesinoxan increased sodium and water excretion to a greater extent in the stroke-prone spontaneously hypertensive rat (SHRSP) than in the Wistar rat (3, 4). Furthermore, in the adult SHR in the established phase of hypertension, Lundin et al. (18), using single-fiber recordings, found renal nerve activity to be elevated compared with that of normotensive controls.

Activity within the renal nerves is determined by the integration of information from a number of sensory sources by the hypothalamic areas of the brain. An important reflex is the baroreceptor reflex, whereby pressure changes within the carotid sinusues and aortic arch lead to inverse responses in renal sympathetic outflow (17). Moreover, the low-pressure atrial stretch receptors, when stimulated either mechanically (14) or after activation of 5-HT$_3$ receptors within the cardiopulmonary areas (24), suppress renal sympathetic nerve activity. There have been reports of visceral sensory receptors in the gut (26), as well as in the kidney itself (15), that can also have an impact in determining the degree of renal nerve activity.

Our early studies showed that stimulation of somatosensory afferent nerves in the brachial plexus of the rat elevated renal sympathetic outflow (11) and caused renal nerve-dependent reductions in renal hemodynamics and fluid output. These functional responses were significantly augmented when the vags were sectioned bilaterally or the carotid sinusues were denervated (5, 6), demonstrating a significant baroreceptor control of this somatosensory reflex on renal sympathetic outflow. By contrast, studies in the SHRSP showed that the ability of somatosensory stimulation to cause an antinatriuresis and antidiuresis was significantly blunted compared with the normotensive rats and appeared to be under exaggerated tonic inhibition by both high- and low-pressure baroreceptors (7). The reasons for these differences in response were unclear, but, with the use of fast-Fourier transformation of the renal sympathetic nerve activity to generate a power spectrum (8), it was found that electric stimulation of the somatosensory nerves caused a reduction in power occurring at the heart rate frequency but increased that appearing at the stimulus frequency. The situation with the SHRSP was very different, insofar as the power occurring at the heart rate frequency was minimally affected by electric stimulation of the somatic afferent nerves (12, 29) but the responses in spectral patterns were partially normalized (28) after vagotomy.

The aim of this study was to gain further information on the importance of the vagal influences in modifying the somatosensory-induced changes in power spectral pattern of the renal nerve activity in both normotensive and hypertensive rats. This was done by stimulating nociceptors of the skin, by locally applying capsaicin to cause reflex activation of the sympathetic nervous system, and by determining how these responses were modified when the cardiopulmonary receptors were...
activated by an infusion of the 5-HT<sub>3</sub> receptor agonist phenylbiguanide (PBG).

**METHODS**

**General Preparations**

All surgical techniques were carried out under the auspices of the United Kingdom Government project license PPL 40/00274 and personal investigator license PIL 40/00371 to E. J. Johns and PIL 40/04186 to T. Zhang.

Male Wistar rats (306 ± 3 g) and SHRSP (306 ± 3 g) rats were fasted but given access to water during the night before use. Anesthesia was induced with a mixture of fluothane-N<sub>2</sub>O-O<sub>2</sub>. A femoral vein was cannulated, and a continuous intravenous infusion of saline (150 mmol/NaCl) was initiated at 3 ml/h; the gaseous anesthetic was gradually (over 30 min) replaced with a urethan-chloralose mixture (180 and 12 mg iv, respectively). Supplemental doses were given at regular intervals every 30 min. A femoral artery was cannulated for monitoring blood pressure (pressure transducer, CEC Instrumentation and amplifier, Grayden Electronics, Birmingham, UK). The animals were tracheotomized and breathed spontaneously. The bladder was cannulated to allow urine to drain, the left kidney was exposed via a retroperitoneal incision, and its ureter was cannulated. The renal nerves were carefully dissected, cleaned, and placed on bipolar stainless steel (Medwire) electrodes. Once a pulsatile signal could be observed, they were sealed in place with Wacker Sil gel 604 (Wacker, Munich, Germany). The animals were allowed 2 h to recover from the surgery.

**Protocols and Animal Groups**

Three groups of Wistar rats were used. Blood pressure, heart rate, and integrated nerve activity were recorded continuously and displayed on a computer throughout the experiment. Each data collection period involved recording a 3.5-min period of blood pressure and renal sympathetic nerve activity that was then stored on the hard disk of the computer.

**Intact group.** As soon as the basal level was recorded, the nociceptors were activated by giving capsaicin (0.15 ml sc of a 1 mg/ml solution made up in absolute alcohol) into each forepaw, and a further 3.5-min collection period was carried out.

**PBG group.** Baseline data were recorded, and, immediately, the cardiopulmonary receptors were stimulated with the use of PBG (Cookson Chemicals, Hampshire, UK) infusion at 32 mg/min iv. Fifteen minutes later the second sample collection was undertaken, which represented the basal measurement before the nociceptor-activating protocol.

**Vagotomy plus PBG group.** The collection period for baseline data was undertaken, after which both vagi were sectioned in the neck region as they ran parallel with the common carotid arteries. After 15 min, a second sample was collected, which represented the baseline against which the cardiopulmonary receptor activation could be compared. The administration of PBG at 32 mg/min iv was begun, and, after a further 15 min, the third sample collection was carried out to obtain the levels for the vagotomized animals in the presence of PBG. The final collection was started immediately after capsaicin was given.

Three complementary groups of SPSHR were used in which the experimental protocols corresponded exactly to the groups of Wistar rats described above.

**Data Analysis in the Time Domain**

The renal sympathetic nerve activity was amplified by means of an optically isolated amplifier (Grayden Electronics) with a gain of 100,000 ×, and high- and low-pass filters were set at 0.1 and 1 kHz, respectively. Both blood pressure and renal sympathetic nerve activity were displayed on a dual-channel oscilloscope and stored on videotape after digitization with a pulse code modulator (Sony PCM-701Es). At the same time, signals from the blood pressure and renal sympathetic nerve channels were relayed to a computer (Apple Macintosh, Centris) and digitized by means of an analog-to-digital converter (National Instrument, NB M10-16H, Austin, TX). A data acquisition program, written in LabVIEW language, was used for online analysis and generated the mean blood pressure, heart rate, and renal sympathetic nerve activity, which was rectified and integrated every 1 s. A mean value was estimated over the 3.5-min collection period for each variable. Thirty minutes after killing the animal, background noise activity was measured in the renal nerves and the values subtracted from the results.

**Data Analysis in the Frequency Domain**

During the final minute of the collection periods, a 1-min high-frequency (1 kHz) sampling of blood pressure and renal nerve activity was taken and stored on the hard disk for off-line processing. The 1-min recording was divided into three 0.5-min 50% overlapping segments. Each of the three segments was further divided in half, and 2° points from each of the six subsegments were passed through a Hanning smoothing window to minimize “end-leakage,” which may result from a finite length of data collection and possible lack of symmetry. The power spectrum was generated, and the relative amount of energy in the renal nerve and blood pressure signals at each frequency, from 0 to 10 Hz in 0.1-Hz increments, was estimated. The total power in the spectrum was calculated as the area under the curve, from 0 to 10 Hz. The power at heart rate frequency was derived by determining the frequency of the maximum peak in the blood pressure recording and the power in the area of the renal nerve spectra that coincided with the heart rate frequency (±0.1 Hz) was taken as the absolute power at heart rate frequency, and the percentage power at heart rate was measured as a proportion of the total power. Cross-correlation analysis between the two signals, blood pressure and renal nerve, was performed to generate phase relationships. The phase difference was derived from the measurement of the real part and imaginary part of the cross power spectrum of the two signals. It indicates the phase lag between two signals, with a difference of 0°, demonstrating synchrony of the two signals, and a difference of 180° that corresponds to a reciprocal relationship between the two signals.

The phase difference only indicates the phase relationship between two signals. However, a change in the heart rate frequency could alter the time difference between the two signals; therefore, the time difference was calculated by

\[
\text{Time difference} = \frac{\text{Phase difference}}{360°} \times \frac{1}{\text{Frequency}} \times 1,000 \text{ ms}
\]

**Statistics**

All data are expressed as means ± SE. The integrated renal sympathetic nerve activity was normalized by expressing the renal nerve activity during the stimulation period as a percentage of the control period immediately before stimula-
tion. The data were analyzed using analysis of variance (ANOVA) and Bonferroni/Dunn post hoc test (Super ANOVA, Abacus, Berkeley, CA) among intact, PBG, and vagotimized and PBG groups. Once within-group differences had been established, the Bonferroni/Dunn post hoc test was applied. The response to a given stimulus was calculated as the difference between the control period immediately before stimulation. Statistical differences were taken when P < 0.05.

RESULTS

**Wistar**

Table 1 gives the basal levels and the responses to capsaicin administration of the cardiovascular variables, integrated renal nerve activity, and the power spectral parameters in the three groups of Wistar rats before and after PBG, vagotomy, and a combination of these maneuvers. It can be seen that after 15 min of PBG infusion there were small increases in blood pressure and heart rate (P < 0.05 and 0.01, respectively), whereas there were decreases in integrated renal nerve activity of ~40% (P < 0.01), total power of ~70% (P < 0.01), and percentage power at heart rate of ~20% (P < 0.05). Both phase and time differences rose by ~30% (both P < 0.01). In the Wistar group subjected to bilateral vagotomy (Table 1), the levels of all variables 15 min after vagotomy were not different from those obtained before section of the nerves. After 15 min of PBG infusion into the vagotomized animals, there was a small rise in heart rate (P < 0.01) and phase and time differences (both P < 0.05), but there was no change in integrated renal nerve activity, total power, or percentage power at heart rate, with these latter responses being significantly different from those induced by PBG in the intact rat. The blood pressure and renal nerve traces of an intact Wistar rat are given in Fig. 1 and show that the subcutaneously administered capsaicin induced a marked increase in both variables, which gradually waned over the remainder of the data collection period. Figure 2 illustrates the blood pressure and renal nerve recordings from one animal and shows that, after a 15-min infusion period, PBG had virtually no effect on blood pressure but caused an obvious suppression of renal nerve activity. Although capsaicin caused a marked but transient increase in blood pressure that fell back toward starting levels over the remainder of the recording period, there was a rise in the renal nerve activity, but it was smaller than that obtained when PBG was not present.

The group data (Table 1) show that capsaicin administration induced significant (P < 0.01 to 0.001) increases in blood pressure and heart rate, the magnitudes of which were very similar in the groups of intact, PBG-treated, and PBG-treated vagotimized rats. Under these conditions, the increases (P < 0.01 to 0.001) in integrated renal nerve activity in the intact and vagotimized animals receiving PBG were similar, but the rise in this variable in the intact animals receiving PBG was much smaller (P < 0.05). A comparison of these changes is illustrated in Fig. 3. Figure 4 shows the power spectral patterns obtained from the renal nerve activity of a Wistar rat and a SHRSP before and during capsaicin administration. It was evident that there was a major peak corresponding to the heart rate frequency and lesser peaks, one of which corresponded to respiration frequency. During the influence of capsaicin, a large increase in the size of the heart rate peak can be seen in the Wistar rat and, to a lesser extent, in the SHRSP. The group data for the power spectra are given in Table 1 and show that capsaicin induced significant increases in the percentage power at heart rate (~3-fold, P < 0.001) and total power (~2-fold, P < 0.001) in both the intact and vagotomized animals given PBG. By contrast, in the intact animals given PBG, the magnitude of increases of percentage power at heart rate and total power were much smaller (P < 0.001 and 0.01, respectively) than those obtained in the two other groups, whereas the increase in phase difference (P < 0.05) was similar to that in the vagotomized animals given PBG. This is illustrated graphically in Fig. 5.

<p>| Table 1. Cardiovascular and renal nerve responses to capsaicin in Wistar rats |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th><strong>BP</strong></th>
<th><strong>HR</strong></th>
<th><strong>RSNA</strong></th>
<th><strong>%Power HR</strong></th>
<th><strong>Total Power</strong></th>
<th><strong>PD</strong></th>
<th><strong>TD</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Intact (n = 8)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>98 ± 5</td>
<td>400 ± 15</td>
<td>5.4 ± 0.4</td>
<td>14 ± 2.8</td>
<td>3.8 ± 0.5</td>
<td>113 ± 13</td>
</tr>
<tr>
<td><strong>Capsaicin</strong></td>
<td>120 ± 6b</td>
<td>424 ± 15b</td>
<td>7.3 ± 0.6e</td>
<td>39 ± 2.8e</td>
<td>8.5 ± 0.8e</td>
<td>130 ± 13</td>
</tr>
<tr>
<td><strong>Intact + PBG (n = 8)</strong></td>
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</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>96 ± 2</td>
<td>392 ± 8</td>
<td>3.7 ± 0.6</td>
<td>15 ± 2.8</td>
<td>1.6 ± 0.4</td>
<td>97 ± 11</td>
</tr>
<tr>
<td><strong>PBG</strong></td>
<td>102 ± 4d</td>
<td>415 ± 15e</td>
<td>2.2 ± 0.4e</td>
<td>12 ± 2.5j</td>
<td>0.5 ± 0.1e</td>
<td>125 ± 10e</td>
</tr>
<tr>
<td><strong>Capsaicin</strong></td>
<td>127 ± 5b</td>
<td>434 ± 11b</td>
<td>3.2 ± 0.6b</td>
<td>24 ± 2.8e</td>
<td>1.4 ± 0.4e</td>
<td>146 ± 7e</td>
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<td><strong>VAG + PBG (n = 8)</strong></td>
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</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>110 ± 2</td>
<td>393 ± 11</td>
<td>5.0 ± 0.7</td>
<td>17 ± 4.3</td>
<td>3.1 ± 1</td>
<td>115 ± 15</td>
</tr>
<tr>
<td><strong>BL VAG</strong></td>
<td>106 ± 6</td>
<td>390 ± 11</td>
<td>4.4 ± 0.6</td>
<td>10 ± 3.8</td>
<td>3.2 ± 1.1</td>
<td>98 ± 10</td>
</tr>
<tr>
<td><strong>PBG</strong></td>
<td>106 ± 5</td>
<td>425 ± 6e</td>
<td>4.0 ± 0.3</td>
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<td>3.1 ± 1.2</td>
<td>122 ± 12j</td>
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<td><strong>Capsaicin</strong></td>
<td>127 ± 6c</td>
<td>443 ± 8b</td>
<td>5.9 ± 0.5e</td>
<td>33 ± 1.5e</td>
<td>8.5 ± 2.9e</td>
<td>150 ± 6e</td>
</tr>
</tbody>
</table>

Values are means ± SE. Blood pressure (BP) in mmHg; heart rate (HR) in beats/min; integrated renal sympathetic nerve activity (RSNA) in mV/s; percentage power at heart rate (% power HR) in %; total power (TP) in W; phase difference (PD) in degrees; and time difference (TD) in ms. Baseline represents value obtained at start of the study. BL-VAG is the level measured 15 min after vagotomy, PBG gives the values obtained after 15 min of phentolamine infusion at 32 μg/min iv, and capsaicin is the value obtained after administration of compound. *P < 0.05; **P < 0.01, and ***P < 0.001 comparison between either PBG or baseline before capsaicin. *P < 0.05; **P < 0.01 comparison between either PBG or baseline before drug.


**SHRSP**

The basal values of the cardiovascular variables and power spectral parameters for the SHRSP groups are given in Table 2. The basal blood pressure and integrated renal nerve activity of the intact SHRSP were significantly higher \((P < 0.001\) and \(0.01\) respectively) compared with the Wistar rats, whereas heart rate was lower \((P < 0.05)\). In terms of the power spectra, only total power was higher \((P < 0.05)\) in the intact SHRSP than in the Wistar. Infusion of PBG (Table 2) caused a \(~10\% (P < 0.01)\) decrease in blood pressure, a \(10\% (P < 0.001)\) increase in heart rate, and a \(20\% (P < 0.01)\) fall in integrated renal nerve activity. This PBG-induced reduction in blood pressure was different from the increase observed in the Wistar rats, although the suppression of integrated renal nerve activity was significantly less \((P < 0.05)\). Furthermore, the infusion of PBG had no effect on total power, percent power at heart rate, and phase and time differences, which contrasted with the reductions in these variables in the Wistar rats (Table 1). After vagotomy (Table 2), there were minimal alterations in the hemodynamic variables and renal nerve characteristics and, thereafter, the administration of PBG for 15 min caused a reduction in blood pressure \((P < 0.001)\) but had no effect on either heart rate or integrated nerve activity, which
In terms of power spectral parameters (Table 2), capsaicin administration to the intact SHRSP caused increases in total power, percent power at heart rate of ~50~70% (P < 0.01 and P < 0.001 respectively), and phase and time differences of ~19% (P < 0.01). Figure 5 shows that the magnitudes of the capsaicin-induced increases in total power were similar in SHRSP and Wistar (6.8 ± 1.7 vs. 4.7 ± 0.7 W), whereas the increases in percent power at heart rate were less in the SHRSP compared with the Wistar (14.5 ± 2.1 vs. 27.5 ± 3.4, P < 0.01). The increases in phase differences were all smaller in the SHRSP compared with the Wistar. Capsaicin administration into the PBG-treated intact SHRSP induced significant (all P < 0.001) increases in total power and percent power at heart rate, the magnitudes of which were not different from those obtained in the intact SHRSP (Table 2). In the vagotomized SHRSP, the response in total power was similar but that in percent power at heart rate was larger (P < 0.05) than in the intact SHRSP (Fig. 5). It was found that, in the intact PBG-treated SHRSP, capsaicin did not change phase difference, whereas in the vagotomized PBG-treated SHRSP, there was an increase in

was different from that observed in the presence of the vagi. The infusion of PBG into the vagotomized SHRSP had no effect on either total power or percent power at heart rate, which was similar to the pattern observed in the intact SHRSP but different from that obtained in the intact Wistar rats, whereas there were decreases (P < 0.001) in phase and time differences.

In the intact SHRSP (Table 2), capsaicin induced increases in blood pressure of ~20% (P < 0.001), heart rate of ~5% (P < 0.001), and integrated renal nerve activity of ~20% (P < 0.01). It was also apparent (Table 2), that in the intact and vagotomized groups of SHRSP given PBG, the magnitudes of the capsaicin-induced increases in blood pressure and heart rate could not be distinguished from the intact group of SHRSP given vehicle, although the increase in integrated renal nerve activity was significantly less (P < 0.01) than that obtained in intact SHRSP. These changes are compared in Fig. 3. The pattern and magnitude of these cardiovascular and renal nerve responses in the SHRSP were very comparable to those obtained in the intact Wistar rats (Fig. 3).
phase difference that was significantly ($P < 0.01$) larger than that obtained in the intact SHRSP (Table 2).

**DISCUSSION**

The aim of this study was to investigate the potential role of the cardiopulmonary receptors in modifying the renal nerve responses to a somatosensory challenge, both normally and in a genetic model of hypertension. Earlier studies in normotensive rats demonstrated that bilateral section of the vagi enhanced the renal nerve functional responses (5, 7) and modulated the renal nerve activity power spectra (6, 12) to another form of somatosensory stimulation, electric activation of the brachial nerve plexi. To explore these findings, two different strategies were adopted. The first entailed stimulating vagal afferent receptors rather than using vagotomy. Veelken and co-workers (24, 25) have provided good evidence to show that there are 5-HT$_3$ receptors within the cardiopulmonary region that, when activated by infusion of PBG either locally into the heart region or systemically, caused transient falls in blood pressure and heart rate but a marked and prolonged decrease in renal sympathetic nerve activity. The second was to selectively activate subcutaneous pain receptors in the forepaw by infiltrating capsaicin, which is recognized to potently cause a depolarization and prolonged activation of sensory receptor endings (13). The dose of capsaicin used in this study was high, but not maximal, and caused an immediate and sustained elevation in blood pressure and renal nerve activity. The possibility exists that some of the capsaicin could have leaked into the circulation where, via vagal afferents, it could exert an inhibitory influence on sympathetic outflow. The contribution that this effect might have on the responses observed could not be quantified. With the use of this approach of local capsaicin administration it was hoped to achieve an activation of a more homogenous population of sensory nerves than that used previously (6, 7, 8), which would have included a range of skin muscle and joint sensory receptors.

**Table 2. Cardiovascular and renal nerve responses to capsaicin in SPSHR**

<table>
<thead>
<tr>
<th></th>
<th>BP</th>
<th>HR</th>
<th>RSNA</th>
<th>%Power HR</th>
<th>Total Power</th>
<th>PD</th>
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<tr>
<td><strong>Intact (n = 8)</strong></td>
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<tr>
<td>Baseline</td>
<td>137 ± 5</td>
<td>309 ± 11</td>
<td>9.4 ± 1.3</td>
<td>27 ± 2.6</td>
<td>9.3 ± 2.4</td>
<td>62 ± 6</td>
<td>32 ± 3</td>
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<tr>
<td>Capsaicin</td>
<td>167 ± 5*</td>
<td>321 ± 10*</td>
<td>11.3 ± 1.5*</td>
<td>41 ± 4.1*</td>
<td>16.1 ± 4.0*</td>
<td>74 ± 7*</td>
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<td><strong>Intact + PBG (n = 8)</strong></td>
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</tr>
<tr>
<td>Baseline</td>
<td>135 ± 6</td>
<td>309 ± 12</td>
<td>7.5 ± 1.5*</td>
<td>24 ± 5.6</td>
<td>4.3 ± 1.3</td>
<td>81 ± 13</td>
<td>46 ± 9</td>
</tr>
<tr>
<td>PBG</td>
<td>123 ± 6</td>
<td>334 ± 12</td>
<td>6.2 ± 1.3</td>
<td>24 ± 2.7</td>
<td>6.8 ± 1.6</td>
<td>84 ± 11</td>
<td>42 ± 7</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>164 ± 8*</td>
<td>359 ± 15*</td>
<td>7.1 ± 1.6*</td>
<td>40 ± 2.7*</td>
<td>12.1 ± 2.3*</td>
<td>91 ± 9</td>
<td>43 ± 5</td>
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<tr>
<td>Baseline</td>
<td>137 ± 7</td>
<td>327 ± 5</td>
<td>10 ± 1.6</td>
<td>19 ± 3.7</td>
<td>6.3 ± 2.5</td>
<td>67 ± 9</td>
<td>34 ± 4</td>
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<tr>
<td>BL-VAG</td>
<td>137 ± 6</td>
<td>332 ± 3</td>
<td>10.2 ± 2.2</td>
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<td>6.2 ± 2.8</td>
<td>81 ± 7</td>
<td>41 ± 4</td>
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<tr>
<td>PBG</td>
<td>111 ± 4*</td>
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<td>9.5 ± 1.9</td>
<td>21 ± 2.0</td>
<td>8.5 ± 3.4</td>
<td>32 ± 8*</td>
<td>18 ± 4*</td>
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<tr>
<td>Capsaicin</td>
<td>134 ± 6*</td>
<td>352 ± 4*</td>
<td>11.2 ± 2.4*</td>
<td>46 ± 5.2*</td>
<td>13.7 ± 3.0*</td>
<td>64 ± 7*</td>
<td>30 ± 3*</td>
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</table>

Values are means ± SE. BP in mmHg; HR in beats/min; integrated RSNA in mV/s; %power HR in %; TP in W; PD in degrees; and TD in ms. Baseline represents value obtained at start of study. BL VAG is the level measured 15 min after vagotomy, PBG gives values obtained after 15 min of PBG infusion at 32 µg/min iv and capsaicin is value obtained after administration of compound. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ comparison between either PRG or baseline before capsaicin. $dP < 0.05$, $eP < 0.01$, $fP < 0.001$ comparison between either PBG and baseline before drug.
The renal nerve activity signal was subjected to fast-Fourier transformation to generate a power spectrum from 0 to 10 Hz in 0.1 Hz increments. It was evident that over this frequency range there was a prominent peak, usually between 6 and 8 Hz, that corresponded to the heart rate frequency, with a smaller peak appearing in the range of the respiration frequency. This power spectral pattern was very similar to that reported previously by us using the anesthetized rat (8, 28, 29) and by others using the conscious rat (21, 9) and rabbit (23), the only difference being that, in the present system, the filters, cut-offs, and frequency ranges were such that the low frequencies, 0.01 to 0.1 Hz, that are of interest in relation to possible autonomic interactions (22), are not evident. The major concern of this present study was the changes in the spectral pattern associated with the heart rate frequency.

Capsaicin administration in the Wistar rat elicited a prompt and sustained rise in blood pressure, heart rate, and integrated renal sympathetic nerve activity. It was apparent from the power spectral parameters that the capsaicin caused an approximate doubling of power within the renal nerve signal, which was even larger (some 3-fold) at the heart rate frequency. These responses would indicate that, during activation of the somatosensory receptors, the impact on the area of the hypothalamus giving rise to the renal sympathetic outflow was such that the increase in nerve traffic occurred primarily at the frequency associated with the heart rate. Interestingly, these changes in spectral pattern differ substantially from those observed in our earlier report in which the brachial nerve plexi were electrically stimulated (8). Under those conditions, integrated renal nerve activity and total power were increased, but within the spectral pattern there was a progressive reduction in the power at heart rate frequency associated with a concomitant rise in power at the frequency at which the brachial nerves were stimulated.

The response to PBG infusion had little effect on blood pressure and heart rate but there was a gradual decrease in integrated nerve activity of ~40–50%, which remained at this lower level throughout the period of PBG infusion. This pattern of responses was similar to that observed by Veelken et al. (24) and has been taken to be due to a cardiorenal reflex (25), whereby activation of the vagal afferent receptors selectively suppresses renal sympathetic outflow. Concomitantly, the infusion of PBG caused a marked decrease in the total power within the renal nerve signal of 70–80%, with a smaller reduction in the percentage of the power occurring at heart rate. This suggests that the organization of the firing rates for the different efferent fibers was reduced and that the nerves were generating action potentials in a more random manner. Despite the PBG infusion, capsaicin still elicited increases in blood pressure and heart rate comparable to those obtained when the compound was not given, but it was evident that the increases in integrated renal nerve activity, total power, and the percentage power at heart rate were markedly attenuated, indicating that the cardiopulmonary receptors were able to selectively diminish and suppress the renal nerve responses to the somatosensory challenge. Nonetheless, it has to be recognized that the high-pressure baroreceptors may make some contribution to these responses, but a limitation of the present approach is that this cannot be quantified. This is because somatosensory receptor activation tends to suppress the carotid baroreflex, and section of the carotid sinus nerves causes a considerable modification of the power spectral pattern making it unsuitable for analysis.

Blood pressure, heart rate, and integrated renal nerve activity were unchanged after vagotomy, which was similar to that observed previously (8, 12), and it is generally accepted that the level of vagal tone is low in the anesthetized rat. Infusion of PBG into the vagotomized animals resulted in a small rise in heart rate, which might indicate some direct effect of the compound either on the heart or within the central nervous system itself (2), although there were minimal effects on integrated renal nerve activity, total power, or percentage power at heart rate. These observations were in marked contrast to the suppression of renal sympathetic nerve activity observed when the vagi were intact, which reinforced the view that the major effects on the PBG were via activation of receptors in the cardiopulmonary region. There were, nonetheless, small increases in both the phase and time differences comparable to those observed in the intact animals, suggesting a nonspecific action of the PBG. Nonetheless, in the PBG-treated vagotomized animals, capsaicin induced increases in blood pressure, heart rate, integrated renal nerve responses, and power spectral parameters virtually identical to those in the intact rats. These findings strengthen the argument that it was afferent input from the cardiopulmonary region carried by the vagi to the central nervous system that attenuated the renal nerve responses to the somatosensory challenge.

There is good evidence that, in the SHR, renal nerve traffic is higher than the normotensive control (18), and the present observations of a higher integrated renal nerve activity in the SHRSP compared with the Wistar suggest that a similar situation pertains in the SHRSP, which is a substrain of the SHR. It was of interest that renal nerve responses, and power spectral parameters virtually identical to those in the intact rats. These findings strengthen the argument that it was afferent input from the cardiopulmonary region carried by the vagi to the central nervous system that attenuated the renal nerve responses to the somatosensory challenge.

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was less. Furthermore, because of the larger baseline levels of both these parameters in the SHRSP, in proportionate terms, the magnitude of the capsaicin-mediated responses were relatively much smaller. Interestingly, in our earlier reports using brachial nerve electric stimulation (12, 28), the responses in spectral pattern were also blunted in the SHRSP. The common feature from these two reports is that the power at heart rate frequency was less able to be altered by the somatosensory challenge and that the oscillator generating the renal nerve output was operating at a much more rigid and fixed level.

Activation of the cardiopulmonary receptors in the SHRSP decreased integrated nerve activity by \(-20\%\), whereas total power increased slightly and the proportion occurring at heart rate remained steady, which was very different from the marked suppression of these parameters in the PBG-treated Wistar. Interestingly, in a preliminary study using 64 \(\mu\)g/min PBG, the hemodynamic or renal sympathoinhibitory responses were of the same magnitude, suggesting a maximal effect of PBG had been achieved. The reasons for this difference are unclear but there is cardiac hypertrophy in the SHRSP (10), which may influence the effectiveness with which the cardiopulmonary receptors are activated by the PBG. Alternatively, the receptors may be defective and, therefore, the reflex renal sympathoinhibition cannot be generated to the same degree. Conversely, it may be that the cardiopulmonary receptors are already activated to a maximal extent and unable to have any further impact on the renal sympathetic outflow generated from the central source.

When the somatosensory challenge was given to the PBG-infused SHRSP, the blood pressure and heart rate responses were unaltered and the increase in integrated renal nerve activity was slightly less. However, the responses in both total power and percentage power at heart rate were unchanged, which contrasted with the marked suppression observed in the Wistar under these circumstances. Again, the fact that the capsaicin-induced increases in power spectral patterns were unaltered during PBG infusion suggests that the cardiorenal reflex was defective, but whether this lies within the heart or centrally remains to be determined. Administration of PBG into vagotomized SHRSP had minor cardiovascular effects but not on either integrated nerve activity or the power spectral characteristics, and the capsaicin-induced response of blood pressure, heart rate, and renal nerve activity were very similar to those obtained in the intact SHRSP. Once again, this set of observations would suggest that, in the SHRSP, the role of vagal afferent information in determining the renal sympathetic nerve responses to the somatic sensory input was limited.

This study set out to define the characteristics of the renal nerve responses after stimulation of the somatosensory system and to determine how these could be modulated by vagal afferent receptors in the cardiopulmonary area. It was apparent that capsaicin caused vasopressor and tachycardic responses in both rat strains. However, integrated nerve activity, the total power, and percentage power at heart rate were markedly raised in the Wistar rat, whereas the changes in power spectral parameters were relatively smaller in the SHRSP. Cardiopulmonary receptor activation in the Wistar rats decreased integrated renal nerve activity, which was associated with loss of power at all frequencies, and the impact of the somatosensory challenge was markedly blunted. By contrast, in the SHRSP the somatosensory challenge caused comparable cardiovascular responses as observed in the Wistar rat, but the changes in renal nerve spectral characteristics were relatively less. Moreover, activation of the cardiopulmonary receptors in the SHRSP had virtually no impact on either the basal pattern of renal nerve activity nor the responses to the somatosensory challenge. These findings suggest that in the SHRSP there were major deficiencies in the vagal influence on the renal sympathetic nerve output, but whether this represents a defect at the heart or within the brain remains to be investigated.

**Perspectives**

The role of the somatosensory system in determining sympathetic outflow to the kidney has received rather less attention than that of the cardiovascular baroreceptors, particularly in regard to the pathophysiological state of hypertension. This study aimed to determine the level of impact that the cardiopulmonary baroreceptors might have on the pattern of renal nerve activity, as assessed from the power spectrum, after a somatosensory challenge. The findings that the somatically induced reflex change in renal nerve activity occurred to a large extent at heart rate frequency complements earlier studies (8) that used a less well-defined stimulus arising from the brachial nerves. Furthermore, in both the present and previous studies (8, 12) it was apparent that the power at heart rate frequency was much less resistant to change, the power increasing nonspecifically along the whole of the spectra, which seemed in part due to exaggerated tonic inhibition from cardiopulmonary receptors. Thus there is a commonality of findings. Exactly why this should occur needs to be resolved. It may be a consequence of either insensitivity to normal baroreceptor input or excessive drive from the low-pressure baroreceptors. Clearly, the neural control of kidney function is increasingly seen as a major determinant of cardiovascular homeostasis, and therefore the impact of these differing patterns of nerve activity or kidney function needs to be addressed.

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**REFERENCES**

RENAL NERVE ACTIVITY IN HYPERTENSION


