Altered frequency characteristics of sympathetic nerve activity after sustained elevation in arterial pressure

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Claassen, Dale E., Richard J. Fels, and Michael J. Kenney. Altered frequency characteristics of sympathetic nerve activity after sustained elevation in arterial pressure. Am. J. Physiol. 274 (Regulatory Integrative Comp. Physiol. 43): R694–R703, 1998.—We tested the hypothesis that sustained elevation in mean arterial pressure (MAP) alters the frequency-domain characteristics of efferent sympathetic nerve discharge (SND) after the return of MAP to control levels. Renal, lumbar, and splanchnic SND were recorded before, during, and after a 30-min increase in MAP produced by phenylephrine (PE) infusion in α-chloralose-anesthetized, spontaneously hypertensive (SH) rats. The following observations were made. 1) The basic cardiac-locked pattern of renal, lumbar, and splanchnic SND bursts was altered after sustained elevation in MAP, demonstrating prolonged effects on the neural circuits involved in entraining efferent SND to the cardiac cycle. Importantly, discharge bursts in afferent baroreceptor nerve activity remained pulse-synchronous after sustained increases in arterial pressure. 2) The frequency-domain relationships between the activity in sympathetic nerve pairs were altered after sustained elevation in MAP, suggesting a transformation from a system of tightly coupled neural circuits to one of multiple generators exerting selective control over SND. 3) The most prominent reduction in SND power after sustained elevation in MAP occurred in the frequency band containing the cardiac cycle, indicating that the prolonged suppression of SND after sustained increases in arterial pressure is due primarily to the selective inhibition of cardiac-related SND bursts. We conclude that sustained elevation in MAP profoundly affects the neural circuits responsible for the frequency components of basal SND in SH rats.

phenylephrine; spontaneously hypertensive rats; aortic depressor nerve activity; autospectral analysis

EFFECTENT SYMPATHETIC NERVE activity is characterized by the presence of synchronized discharge bursts. In baroreceptor-innervated animals, efferent sympathetic nerve activity can contain cardiac, respiratory, and low-frequency (less than central respiration) oscillations (5, 8, 9, 11, 16, 22, 23, 29, 32, 38). Power density spectral analysis reveals a prominent peak at the frequency of the cardiac cycle in anesthetized animals with intact arterial baroreceptors (8, 14, 16, 22, 25). Coherence analysis reveals a strong correlation between the cardiac cycle and the basal discharges of sympathetic nerves innervating different regional circulations (9, 16, 22, 23). In baroreceptor-denervated animals, sympathetic nerve discharge (SND) bursts are not coupled to the arterial pulse, demonstrating that the cardiac-related frequency component in sympathetic nerve activity is dependent on the presence of arterial baroreceptors (9, 14, 17). These observations indicate that the cardiac-related pattern of synchronized SND bursts reflects the fundamental organization of those neural circuits responsible for basal sympathetic nerve outflow in baroreceptor-innervated animals.

The cardiac-related pattern of SND, however, can be altered during specific behavioral states and by periods of acute physical stress. Hyperthermia in chloralose-anesthetized rats can transform the basic pattern of renal SND from one containing a primary peak at the frequency of the cardiac cycle to one exhibiting a slow periodicity at or near the frequency of ventilation (18). Body movement and excitement in awake cats increases the probability of cardiac sympathetic nerve activity at 8–12 Hz and reduces the probability of activity at or near the frequency of the cardiac cycle (31). Cerebral ischemia and asphyxia (16, 25, 26) reduce the occurrence of cardiac-related synchronized discharge bursts and increase the presence of high-frequency activity in renal, inferior cardiac, and vertebral nerves. These results provide examples of functional plasticity in the neural circuits involved in the generation of sympathetic nerve activity and suggest that the neural circuits responsible for basal SND are capable of generating different activity patterns depending on the physiological state of the animal.

In recent studies (3, 21), we demonstrated that the regulation of efferent sympathetic nerve activity in spontaneously hypertensive (SH) rats is altered after sustained elevation in arterial pressure. Specifically, the activity in numerous sympathetic nerves (renal, adrenal, lumbar, splanchnic) remains significantly reduced from control values after sustained phenylephrine (PE)-induced increases in mean arterial pressure (MAP), despite the return of arterial pressure to control levels. Moreover, the duration of the adrenal and splanchnic sympathoinhibitory responses after sustained elevation in MAP is significantly less than that in the renal and lumbar nerves, demonstrating that the poststimulus responses of efferent SND are regionally nonuniform. Although these results indicate that sustained increases in MAP have a profound and prolonged effect on sympathetic regulatory mechanisms in SH rats, the influence of sustained increases in MAP on the frequency components in efferent SND has not been determined. This is a significant omission because alterations in the basic SND bursting pattern may provide the key for understanding mechanisms by which sustained increases in arterial pressure affect the efferent limb of the baroreflex.

In the present study, we tested the hypothesis that the frequency-domain characteristics of efferent SND in SH rats are altered after sustained elevation in arterial pressure and the return of arterial pressure to control levels. Activity was recorded from the renal, lumbar, and splanchnic sympathetic nerves. Autospectral and coherence analyses were used before and after

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PE-induced increases in MAP to characterize the frequency components in SND and the frequency-domain relationships between the activity in different sympathetic nerves. SH rats were used because the sympathetic nerve responses after sustained baroreceptor afferent stimulation are more prolonged in SH rats than in Wistar-Kyoto (WKY) rats (Ref. 21 and this study). Our results demonstrate that sustained elevation in arterial pressure in SH rats profoundly alters the pattern of basal SND and uncouples the sources of synchronized discharges in different sympathetic nerves, a means by which the central nervous system may generate nonuniform sympathetic nerve responses. In addition, our results demonstrate that sustained increases in MAP selectively reduce sympathetic nerve activity at the frequency of the cardiac cycle, a reduction that strongly contributes to the altered pattern and prolonged inhibition of SND.

METHODS

General Procedures

The surgical procedures and experimental protocols used were approved by the Institutional Animal Use and Care Committee. Experiments were performed on male SH and WKY rats (250–350 g). Anesthesia was initially induced with methohexital sodium (Brevital, 50–60 mg/kg ip). Two catheters (polyethylene-10 and polyethylene-50) were placed in the femoral vein. The polyethylene-10 catheter was used during the surgical preparation for administration of small maintenance doses of methohexital sodium and during the experimental protocols for administration of drugs. The polyethylene-50 catheter was used for the administration of an initial dose of α-chloralose (50 mg/kg) and for maintenance doses (25–35 mg·kg⁻¹·h⁻¹) throughout the surgical preparation and experiment. The trachea was cannulated with a polyethylene-240 catheter, and the rats were allowed to breathe oxygen-enriched air spontaneously. Femoral arterial pressure and heart rate (HR) were recorded using standard procedures. Core body temperature was measured with a thermistor probe inserted ~5–6 cm into the colon and was kept between 37.5–38.0°C by a temperature-controlled surgical table.

Sinoaortic denervation (SAD) in 10 SH rats was completed using the method described by Krieger (27). Briefly, the aortic arch was denervated by sectioning the superior laryngeal nerve near its junction with the vagus nerve and removing the superior cervical ganglion. The carotid sinus was denervated by removing the adventitia from the carotid sinus bifurcation and applying 10% phenol to the area. Baroreceptor denervation was indicated by the absence of sympathoinhibition during increases in arterial pressure produced by a bolus injection of PE (4–5 µg/kg·iv) and by the loss of coherence between the arterial pulse and SND (14, 17).

Lateral ventricular cannulae used for the intracerebroventricular administration of PE were surgically implanted in six SH rats. Anesthetized (Brevital and chloralose as described above) rats were placed in a stereotaxic frame. With the head leveled between lambda and bregma, a small hole was made in the skull 1 mm lateral to the midline and 1 mm caudal to bregma (19). A 10-mm stainless steel cannula (23 gauge) was lowered 5 mm below the surface of the skull and fixed in place using dental cement. Lateral ventricular cannulation was indicated by the appearance of cerebral spinal fluid in the cannula, 2) an increase in arterial pressure after the intracerebroventricular injection of angiotensin II (4 µg), and 3) the presence of india ink in the ventricular system after intracerebroventricular administration after the experimental protocol.

Neural Recordings

Sympathetic activity was recorded biphaseically with a platinum bipolar electrode after capacity-coupled preamplification (band pass 30–3,000 Hz) from the central end of cut or distally crushed renal, splanchnic, and lumbar sympathetic nerves. The left renal and splanchnic nerves were isolated either retroperitoneally or after a midline laparotomy. The left lumbar nerve was isolated from a midline approach. The nerve-electrode preparations were covered with a silicone gel to prevent exposure to room air. The sympathetic nerve potentials were full-wave rectified and integrated (time constant 10 ms), which produced a smooth tracing of the synchronized discharges. SND was quantified as volts × seconds. The sympathetic nerve recordings were corrected for background noise at the end of the experiment after administration of the ganglionic blocker, trimethaphan camsylate (10–15 mg/kg·iv).

The aortic depressor nerve (ADN) was isolated from a ventral approach ~1–2 cm caudal to its junction with the superior laryngeal nerve. Baroreceptor nerve activity was recorded from the ADN because this nerve contains only baroreceptor afferents in the rat (30, 33). ADN potentials were full-wave rectified and integrated (time constant 10 ms; band pass 30–3,000 Hz) or recorded after wide-band (1–1,000 Hz), capacity-coupled preamplification. ADN activity was quantified as volts × seconds. ADN recordings were corrected for background noise after the distal end of the nerve was crushed after the experiment.

Experimental Protocols

After surgery, the chloralose-anesthetized rats were allowed to stabilize for 30–60 min before initiation of the experimental protocols.

Protocol 1. To determine the influence of sustained elevation in MAP on the basic pattern of SND bursts, autospectral analysis of renal (n = 7), splanchnic (n = 6), and lumbar (n = 6) SND and arterial pressure was completed before and after infusion of PE in baroreceptor-innervated SH rats. In addition, autospectral analysis of SND was completed before and after PE infusion in six baroreceptor-denervated WKY rats (renal, n = 6) and in 10 baroreceptor-denervated SH rats (renal, n = 4, lumbar, n = 2, splanchnic, n = 4). The following protocol was performed once on each animal. MAP, HR, and SND were recorded during 1) 30 min of control; 2) 30 min of intravenous PE infusion (5–20 µg·kg⁻¹·min⁻¹), which increased MAP 40–50 mmHg and produced sympathoinhibition (85–100%); and 3) during 15–40 min of recovery after the cessation of PE infusion. Recovery measurements were initiated at the point MAP stabilized to control levels (3 ± 0.4 min after cessation of PE infusion), and this initial measurement period was designated R1. A second measurement period during recovery was recorded 5 min after R1 and was designated R2. Control experiments were completed in which MAP and renal (n = 4), splanchnic (n = 4), and lumbar (n = 2) SND were recorded throughout identical time periods before, during, and after the infusion of the saline vehicle (0.9% NaCl; 3–10 µl/min·iv).

Protocol 2. To determine the influence of sustained elevation in MAP on the frequency-domain relationships between activity in different sympathetic nerves, the coherence analysis of discharges in renal-splanchnic (n = 2) and renal-lumbar (n = 4) nerve pairs was completed before and after PE infusion. In one experiment, coherence analysis relating the discharges in renal and lumbar nerves was completed after infusion of the saline vehicle.
Protocol 3. To examine the central action of PE on the frequency components in SND, autospectral analysis of renal SND was completed before and up to 30 min after the administration of either saline vehicle (0.9% NaCl, 3 µl) or PE (1, 3, 6, and 10 µg dissolved in 3 µl saline) into the lateral ventricle in SH rats with intact arterial baroreceptors (n = 6).

Protocol 4. To examine the influence of sustained PE-induced increases in MAP onafferent baroreceptor nerve activity, autospectral analysis of ADN pulse-synchronous activity was completed before, during, and after infusion of PE in five SH rats. The experimental protocol was identical to that described in protocol 1.

Protocol 5. To determine if the prolonged reduction of sympathetic nerve activity from control levels after a sustained increase in arterial pressure involves the inhibition of activity in specific frequency components in the sympathetic signal, the amount of power in individual 3-Hz frequency bands (0–3 Hz and 6–9 Hz) was quantified in the renal (n = 7), splanchnic (n = 6), and lumbar (n = 6) SND recordings from protocol 1 before and after infusion of PE.

Data Analysis

Autospectral and coherence analyses of the arterial pulse, ADN discharge, and SND were computed using methods and programs described earlier (24). The signals were low-pass filtered at 100 Hz and sampled at 250 Hz. Fast Fourier transformation was performed on 16–20 contiguous windows of data that were 5 s in duration. Autospectra and coherence functions were computed over a frequency band of 0–50 Hz. Amplitudes of the autospectra were autoscaled to the highest peak (22). The percent of total power in SND in individual 3-Hz frequency bands (0–3 Hz and 6–9 Hz) was quantified after autospectral analysis using the program of Kocsis et al. (24). The amount of power (V x s) in these frequency bands was quantified after autospectral analysis.

Spectral analyses provide the following information (24). The autospectrum of a signal shows the relative power present at each frequency. The coherence function (normalized cross spectrum) provides a measure of the strength of linear correlation of two signals at each frequency. The squared coherence value (referred to as coherence value) is 1.0 in the case of a linear system undisturbed by noise, and zero if the two signals are completely unrelated.

Control values of SND were taken as 100%. Values in the text, Table 1, and Fig. 8 are means ± SE. Statistical analysis was performed using a two-factor repeated-measures analysis of variance (ANOVA). The overall analysis was followed by Bonferroni pairwise post hoc tests to compare the two groups at each time point and to compare different time points within each group. P < 0.05 indicated statistical significance.

RESULTS

Protocol 1: Effects of Sustained Elevation in Arterial Pressure on the Basic Pattern of SND

The influence of PE-induced sustained elevation in arterial pressure on the pattern of SND bursts after the return of arterial pressure to control levels was determined in 19 experiments (renal SND, n = 7, splanchnic SND, n = 6; lumbar SND, n = 6). MAP values increased 40–50 mmHg for the 30 min of PE infusion and returned to control levels after PE infusion (control, 156 ± 4 mmHg; R1, 156 ± 4 mmHg; R2, 155 ± 4 mmHg). In each of the 19 experiments, the basic cardiac-related bursting pattern of SND was markedly altered during recovery after cessation of PE infusion and the return of arterial pressure to control levels.

Figure 1 shows renal (top traces), lumbar (middle traces), and splanchnic (bottom traces) SND slow waves and pulsatile arterial pressure traces from three experiments recorded before (control) and after (recovery) a 30-min PE-induced increase in arterial pressure. MAP values returned to control levels during the recovery period after PE infusion. During control, the majority of SND bursts were coupled to the arterial pulse, with the rising phase in SND slow waves generally occurring after the peak increase in systolic arterial blood pressure. As expected (3, 21), the level of activity in all three nerves was inhibited (85–100%) from control levels during the infusion of PE and gradually recovered but remained below control levels during the period after PE infusion. The pattern of SND bursts during the recovery, however, was not characterized by the presence of reduced-amplitude, cardiac-locked bursts. In fact, the sympathetic nerve activity pattern during recovery after sustained elevation in arterial pressure was characterized by wide-band SND bursts lasting several cardiac cycles, multiple bursts in single cardiac cycles, discharge bursts that were unchanged by the peak increase in systolic arterial blood pressure, and bursts that were uncoupled from the cardiac cycle.
The results of autospectral analysis of the SND bursting pattern from three SH rats are shown in Fig. 2, A–C. Renal, lumbar, and splanchnic SND autospectra were constructed before (control) and after (R1, R2) sustained PE-induced increases in MAP in 3 SH rats. D: autospectra of renal SND before and after PE infusion in a normotensive Wistar-Kyoto (WKY) rat. R1, recovery period after cessation of PE infusion at the point mean AP returned to control levels; R2, recovery period 5 min after R1. Amplitudes of the autospectra are autoscaled to the highest peak. Frequency band is displayed from 0 to 15 Hz.

The results of autospectral analysis of the SND bursting pattern from three SH rats are shown in Fig. 2, A–C. Renal, lumbar, and splanchnic SND autospectra were constructed before (control) and after (R1, R2) 30-min PE-induced increases in MAP. During control, the autospectrum of activity in each nerve contained a primary peak at the frequency of the heart rate (renal SND, 6.8 Hz; lumbar SND, 6.4 Hz; splanchnic SND, 6.8 Hz), demonstrating a prominent contribution of cardiac-related SND bursts to the basal sympathetic signal. In contrast, autospectra of renal, lumbar, and splanchnic SND constructed at R1 (3 ± 0.4 min after cessation of PE infusion) did not exhibit a primary peak at the frequency of the heart rate (renal SND, 7.0 Hz; lumbar SND, 6.8 Hz; splanchnic SND, 6.8 Hz) despite the return of arterial pressure to control levels. In fact, the primary peaks in these autospectra at R1 were contained between 0 and 3 Hz. At R2 (5 min after R1), the shape and contour of the splanchnic SND autospectrum (Fig. 2C) indicated a return of cardiac-related activity similar to control. The renal SND autospectrum (Fig. 2A) also exhibited a cardiac-related peak at R2, although peaks representing relative power at lower frequencies remained well above control levels. The lumbar SND autospectrum (Fig. 2B) at R2 continued to display a primary peak between 0 and 3 Hz, with little indication of activity at the frequency of heart rate (6.8 Hz). In some experiments, lumbar SND autospectra during control did not contain the primary peak at the frequency of the cardiac cycle; nevertheless, relative power decreased at the cardiac-related frequency and increased at frequencies between 0 and 3 Hz after sustained increases in MAP. Similar poststimulus changes, in which the relative power in renal, lumbar, and splanchnic SND autospectra at R1 was shifted from the frequency of the cardiac cycle to frequencies <3 Hz, were observed in all 19 experiments.

Figure 2D shows the results from an experiment in which autospectral analysis was completed on renal SND in a WKY rat before (control) and after (R1, R2) a 30-min PE-induced increase in MAP and the return of MAP to control levels (control, 118 ± 9 mmHg; R1, 120 ± 9 mmHg; R2, 119 ± 10 mmHg). During control, the renal SND autospectrum contained a primary peak at the frequency of the heart rate (6.8 Hz). Similar to the results from SH rats, at R1 the renal SND autospectrum in the WKY rat contained a primary peak between 0 and 3 Hz. However, a cardiac-related peak was clearly present at R1, and, by R2, the WKY renal SND autospectrum was similar to control. Similar changes in the renal SND autospectrum were observed in eight WKY experiments.

Figure 3 shows the results of autospectral analysis of renal SND from an SH rat before (control) and after (R1, R2) a 30-min infusion of the saline vehicle. Note that the autospectra constructed during recovery after saline infusion were very similar to the control autospectrum, demonstrating that poststimulus changes in the renal SND autospectrum were in SH rats. R1, recovery period after cessation of PE infusion at the point mean AP returned to control levels; R2, recovery period 5 min after R1. Amplitudes of the autospectra are autoscaled to the highest peak. Frequency band is displayed from 0 to 15 Hz.
frequency characteristics of SND after PE infusion are not due to volume or time effects. Similar results were observed in 10 control experiments (renal, n = 4; lumbar, n = 2; splanchnic, n = 4).

To examine the influence of PE infusion and sustained MAP elevation on the noncardiac-related components in SND, autospectral analysis of SND was completed in 10 SH rats after SAD. Figure 4 shows the results of a representative experiment in which renal SND autospectra were constructed before (control) and after (R1, R2) sustained PE-induced increases in MAP. In baroreceptor-denervated rats, the SND autospectra during control exhibited a broad band frequency distribution with an absence of a peak at the frequency of the cardiac cycle (6.8–7.2 Hz). Importantly, in the absence of baroreceptor afferents, the autospectra after sustained increases in arterial pressure remained unchanged from control. In all 10 baroreceptor-denervated SH rats (renal, n = 4; lumbar, n = 2; splanchnic, n = 4), the percentage of total power in individual 3-Hz frequency bands remained unchanged during control, PE infusion, and recovery (Table 1). Because there were no significant differences between the responses of renal, lumbar, and splanchnic SND in these experiments, the data were combined for presentation.

Protocol 2: Effects of Sustained Elevation in Arterial Pressure on the Frequency-Domain Relationships Between the Discharge Patterns in Sympathetic Nerve Pairs

The relationships between simultaneously recorded discharges of sympathetic nerve pairs before and after PE infusion were analyzed in SH rats using the coherence function in six experiments (renal-splanchnic, n = 2; renal-lumbar, n = 4). In five experiments the peak coherence value relating the activity in sympathetic nerve pairs was significantly reduced, from 0.87 ± 0.03 during control to 0.45 ± 0.13 at R1. The peak coherence value returned to control levels (0.72 ± 0.09) at 20 ± 7 min of recovery. Figure 5 shows the results of autospectral and coherence analyses of SND bursts from a representative experiment before (control) and after (R1, R2) sustained increases in MAP. Figure 5 shows renal (Fig. 5A) and lumbar (Fig. 5B) SND autospectra, and Fig. 5C shows nerve-to-nerve coherence functions. During control, the renal SND autospec-

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<th>Frequency Band, Hz</th>
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Values are means ± SE; n = 10. SAD, sinoaortic denervation; SH, spontaneously hypertensive; SND, sympathetic nerve discharges; R1, recovery period at which mean arterial pressure returned to control levels after cessation of phenylephrine (PE) infusion; R2, recovery period 5 min after R1. Individual frequency bands represent combined data from renal (n = 4), splanchnic (n = 4), and lumbar (n = 2) nerve recordings.
trum contained a primary peak at the frequency of heart rate, and the autospectrum of lumbar SND showed two distinct peaks, one at the cardiac-related frequency and one at a frequency <3 Hz. Coherence analysis of renal and lumbar SND during control demonstrated strong coupling at the cardiac-related peak and at the low-frequency peak as shown by peak coherence values of 0.87 and 0.85, respectively. However, during recovery from sustained elevation in MAP, there was reduced coupling between the discharges in the renal and lumbar nerves, as evidenced by marked reductions in coherence, despite the fact that these nerves showed similar poststimulus changes in the pattern of SND bursts.

In contrast to the five experiments described above, in one experiment the peak coherence value (control, 0.98; R1, 0.95; R2, 0.96) and the coherent frequency band relating the discharges in a renal-splanchnic nerve pair did not differ between control and recovery.

In a time- and volume-control experiment, peak coherence values relating the discharges in a renal and splanchnic nerve pair remained unchanged from control values after vehicle infusion (control, 0.9; R1, 0.97; R2, 0.97).

Protocol 3: Direct Actions of PE on the Cardiac-Related Frequency Components in SND

To determine if changes in the basic pattern of SND after PE-induced increases in MAP result from a direct effect of PE on the central neural circuits responsible for generation of SND, autospectra of renal SND were constructed before and up to 30 min after the injection of PE (1, 3, 6, and 10 µg, 3 µl) or vehicle (saline, 3 µl) into the lateral ventricle of six SH rats with intact baroreceptors. In all experiments, MAP remained unchanged from control levels after intracerebroventricular administration of PE. Results from a representative experiment are shown in Figure 6. During control, the renal SND autospectra contained a primary peak at the frequency of the cardiac cycle. After intracerebroventricular PE administration, the renal SND autospectra and arterial blood pressure remained unchanged from control. Importantly, the central administration of PE at doses between 1 and 10 µg did not alter the basic pattern of SND bursts in any of the six experiments completed. The SND bursting pattern also remained unchanged from control levels after the intracerebroventricular sympathetic administration of vehicle (n = 6).

Protocol 4: Effects of PE-Induced Increases in Arterial Pressure on Pulse-Synchronous Discharges in Afferent Baroreceptor Nerve Activity

To determine if changes in the SND bursting pattern after PE-induced elevation in MAP result from changes in the pulse-synchronous discharge characteristics of afferent baroreceptor nerve activity, ADN activity was recorded simultaneously with SND (renal, n = 3; lumbar, n = 2) in five SH rats before, during, and after a 30-min infusion of PE. Figure 7 shows the results of one representative experiment in which autospectra of renal SND (Fig. 7A), ADN activity (Fig. 7B), and arterial blood pressure (Fig. 7C) were recorded.
pulsatile arterial pressure (Fig. 7C) were constructed before (control) and after (R1, R2) PE-induced increases in MAP. During control, the autospectra of SND, ADN activity, and arterial pressure contained primary peaks at the frequency of the heart rate. After sustained PE infusion and the return of MAP to control levels, the primary peak in the renal SND autospectra was contained between 0 and 3 Hz. In contrast, the primary peak in the ADN autospectrum remained at the frequency of heart rate after PE infusion. Importantly, in the five experiments completed, the pulse-synchronous pattern of ADN bursts was maintained after sustained elevation in arterial pressure and the return of arterial pressure to control levels.

Protocol 5: Effects of Prolonged Increases in Arterial Pressure on SND Power in Selective Frequency Bands

To determine the influence of sustained elevation in arterial pressure on the amount of activity in selected SND frequency bands, we quantified the activity in individual 3-Hz frequency bands before and after sustained PE-induced increases in MAP. Figure 8 summarizes the results of this analysis for the 0- to 3-Hz and 6- to 9-Hz frequency bands for renal (n = 7), lumbar (n = 6), and splanchic (n = 6) SND. These frequency bands were analyzed because 70–80% of the total power in SND is located in the 0- to 3- and 6- to 9-Hz frequency bands. Two points are worth noting. First, under control conditions, cardiac-related nerve activity (6–9 Hz) contributes a large amount of power to renal and splanchic SND (Fig. 8, A and C) whereas lower frequency, noncardiac-related nerve activity (0–3 Hz) contributes equally with cardiac-related activity to lumbar SND (Fig. 8B). Second, SND power in the cardiac-related (6–9 Hz) but not the noncardiac-related (0–3 Hz) frequency band was significantly reduced from control levels throughout the recovery period. Specifically, the SND power in the 6- to 9-Hz frequency band at R1 was reduced from control values −79%, −75%, and −64%, respectively, in renal, lumbar, and splanchic nerves. At R2, the power in the 6- to 9-Hz frequency band remained reduced from control values in renal, lumbar, and splanchic SND (−63%, −58%, −35%, respectively). In contrast, power in the 0- to 3-Hz frequency band was reduced at R1 (−30%) only in renal SND, and no significant reduction in SND power was observed in the 0- to 3-Hz band at R2. Note that the major decreases in SND power after PE infusion were contained in the 6- to 9-Hz frequency band and occurred despite the return of MAP to control levels (control, 156 ± 4 mmHg; R1, 156 ± 4 mmHg; R2, 155 ± 4 mmHg) and despite the fact that heart rate remained in this frequency band (control, 6.9 ± 0.1 Hz; R1, 7.4 ± 0.1 Hz; R2, 7.1 ± 0.1 Hz).

DISCUSSION

The results of the current study demonstrate that sustained PE-induced increases in arterial pressure have profound and prolonged effects on the neural circuits responsible for basal SND in SH rats. Three observations support this conclusion. First, the fact that the basic cardiac-locked pattern of renal, lumbar, and splanchic SND bursts was profoundly altered after sustained elevation in MAP despite the presence of pulse-synchronous activity in arterial baroreceptor afferents demonstrates changes in the neural circuits responsible for generation of cardiac-related efferent SND bursts. Second, the sources of synchronized discharges in different sympathetic nerves were uncoupled after sustained increases in arterial pressure as demonstrated by significant reductions in the coherence values relating the discharges in sympathetic nerve pairs. Third, the most prominent and prolonged reduction in the sympathetic nerve signal during recovery after PE infusion occurred in the frequency band
containing heart rate (6–9 Hz), indicating that the suppression of efferent SND, which persists after sustained elevation in arterial pressure (3, 18), is due primarily to the selective inhibition of cardiac-related bursts.

In baroreceptor-innervated animals, the cardiac-related rhythmicity in efferent SND reflects the fundamental organization of those neural circuits responsible for basal sympathetic outflow. The current results from SH rats demonstrate that after sustained elevation in arterial pressure the cardiac-related bursting pattern is fundamentally altered. Specifically, the post-stimulus SND pattern is characterized by the presence of sympathetic nerve bursts that are not coupled to the arterial pulse, an absence of bursts during numerous cardiac cycles, and the presence of multiple bursts within a given cardiac cycle. These poststimulus changes in the SND pattern are particularly striking, considering that levels of arterial pressure were the same before and after PE infusion, that ADN discharge bursts remained pulse-synchronous after sustained increases in arterial pressure, and that ADN activity is not reduced after sustained PE infusion (20, 21). The current findings are consistent with stimulation-induced changes in the neural circuits involved in coupling afferent baroreceptor nerve activity and efferent SND. If sustained elevation in arterial pressure had simply inhibited sympathetic nerve activity without concomitant changes in the neural circuits responsible for coupling sympathetic nerve activity to the cardiac cycle, poststimulus sympathetic nerve outflow would be characterized by low-amplitude, cardiac-related bursts. This was not the case, however, as the frequency characteristics of SND were altered after sustained increases in arterial pressure in each of the 19 SH rat experiments completed. In addition, the SND bursting pattern was altered (although transiently) after sustained elevation in arterial pressure in WKY rats, demonstrating that poststimulus changes in the neural circuits responsible for generation of cardiac-related SND bursts are not strictly related to the strain of rat or to the resting level of arterial pressure.

In addition to the prominent cardiac-related component in basal SND in baroreceptor-innervated rats, there is also activity in the sympathetic nerve signal at frequencies lower than that of the cardiac cycle. While both cardiac- and noncardiac-related components in SND were reduced from control values during PE-induced increases in arterial pressure, a selective inhibition of cardiac-related SND bursts was evident during recovery after the return of arterial pressure to control levels. As stated previously, we (3, 21) and others (12, 13, 15, 28, 37) have reported that sustained activation of arterial baroreceptor afferents (either by increases in arterial pressure or electrical stimulation of afferent baroreceptor nerves) induces prolonged inhibition of SND, which persists after the cessation of baroreceptor afferent stimulation. Importantly, the current results demonstrate that the prolonged inhibition of efferent sympathetic nerve activity after sustained increases in MAP in SH rats is mediated primarily by the selective inhibition of cardiac-related SND bursts. The results of previous studies by Barman and colleagues (1, 2) suggest that the pattern of SND is the emergent property of different pools of brain stem neurons that are linked to noncardiac or cardiac-related rhythms. Importantly, the discharges of brain stem neurons with activity correlated to either noncardiac- or cardiac-related rhythms in SND are influenced by activation of the arterial baroreceptor reflex (2). Relative to the current results, sustained activation of baroreceptor afferents may produce prolonged central neural alterations that reduce the probability of brain stem neurons with cardiac-related activity to contribute to efferent SND.

It is unlikely that poststimulus changes in the SND bursting pattern resulted from a direct effect of PE on the central neural circuits responsible for SND, as the intracerebroventricular administration of PE in SH rats did not alter either cardiac- or noncardiac-related components of SND or the basal level of nerve activity. These findings are particularly interesting when considered with respect to the results of Imaizumi et al. (15), who reported that the intracerebroventricular administration of PE in anesthetized rabbits enhances the gain of the baroreflex control of efferent SND. Taken together, these results suggest that the baroreflex control of efferent sympathetic nerve activity and the entrainment of SND to the cardiac cycle by afferent baroreceptor nerves may be dissociated under certain experimental conditions, demonstrating a high level of functional complexity in the arterial baroreceptor reflex regulation of sympathetic nerve outflow. The experimental demonstration of a functional dissociation between baroreflex control of efferent sympathetic nerve activity and generation of cardiac-related SND bursts may have an important pathophysiological corollary, as the baroreflex regulation of efferent SND is impaired in heart failure, despite the fact that sympathetic nerve activity is characterized by a prominent cardiac rhythmicity (6, 7).

The current results indicate that the neural sources of synchronized SND in different sympathetic nerves uncouple after sustained increases in arterial pressure in SH rats, as evidenced by reductions at both cardiac- and noncardiac-related frequencies in the coherence values relating the discharges in sympathetic nerve pairs. A reduction in the coherence relationship between two sympathetic nerves would suggest that the activity recorded in these nerves after sustained elevations in arterial pressure does not simply involve the signature output of a single central neural generator but rather involves the transformation to a central system of multiple generators exerting selective control over postganglionic SND. As stated previously, the duration of the sympathoinhibition after PE-induced increases in MAP is regionally nonuniform (3). Uncoupling of the frequency components in SND may provide the neural substrate for generating nonuniform poststimulus responses. Alternatively, or in addition, uncoupling of the frequency components in SND may be an important means by which the central nervous system
fine tunes the regulation of sympathetic outflow to selective regional circulations after prominent changes in the level of total activity. Although the coherence function provides a measure of the strength of the linear correlation of the sympathetic signals at each frequency (24), it cannot detect frequency-domain relationships that are based on nonlinearities or differential gating or filtering. Such nonlinear correlations may exist in the frequency-domain relationships between the discharges of sympathetic nerve pairs after sustained PE-induced increases in arterial pressure.

Perspectives

The sympathetic nervous system plays a critical role in the regulation of vasomotor activity and cardiovascular function. Because sympathetic nerve dysfunction contributes importantly to many disorders of cardiovascular function (including hypertension) (35), it is important to understand mechanisms involved in sympathetic nerve regulation. Important functional characteristics of SND include the background level of activity, synchronized discharges of efferent activity, and the formulation of differentiated patterns of sympathetic outflow during various physiological states. Central neural mechanisms involved in mediating the functional characteristics of SND are not well established. The results of the current study and others from this laboratory (3, 21) demonstrate that sustained activation of arterial baroreceptor afferents markedly influences each of these functional characteristics of SND. Specifically, after cessation of PE infusion and the return of arterial pressure to control levels, efferent SND (renal, adrenal, splanchnic and lumbar) remains significantly reduced, the basic pattern of SND is altered, and the duration of the sympathoinhibitory responses are regionally nonuniform. SAD eliminates each of these poststimulus changes, implicating a role for afferent baroreceptor mechanisms in mediating these responses. Importantly, because much information is known about the central neural pathways and neurotransmitters involved in baroreflex regulation (4, 10, 34, 35, 36), future studies designed to determine the central norocircuity involved in mediating poststimulus sympathetic nerve responses will likely provide key information for understanding the control of efferent sympathetic nerve outflow.

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REFERENCES


