Basis for phase relations between baroreceptor and sympathetic nervous discharge

GERARD L. GEBBER
Department of Pharmacology, Michigan State University, East Lansing, Michigan 48824

Gebber, Gerard L. Basis for phase relations between baroreceptor and sympathetic nervous discharge. Am. J. Physiol. 230(2): 263-270. 1976. The phase relations between the cardiac cycle and sympathetic nervous discharge (SND) were studied with an average-response computer in the anesthetized cat. Maximum SND occurred during early diastole at heart rates between 3 and 4 beats/s. Dramatic shifts in the phase relations between SND and the cardiac cycle accompanied the decrease in heart rate produced by stimulation of the distal end of the cut right vagus nerve. The point of maximum SND was shifted from early diastole to near peak systole and then into the late diastolic phase of the preceding cardiac cycle as heart rate was progressively lowered to 2 beats/s. These observations indicate that synchronization of SND during each cardiac cycle is not the simple consequence of the waxing and waning of baroreceptor nerve activity. Rather, 1:1 locking of bursts of SND to the cardiac cycle is explained on the basis of entrainment by the baroreceptor reflexes of a sympathetic rhythm of central origin. An inhibitory-phasing hypothesis is proposed to account for entrainment. In addition, two components (spinal and brainstem) of sympathoinhibition associated with the pulse-synchronous discharge of the carotid sinus nerve were revealed when the 1:1 relationship between bursts of SND and the cardiac cycle was disrupted at heart rates below 2 beats/s.

inhibitory phasing; spinal inhibition; brainstem inhibition

SPONTANEOUSLY OCCURRING DISCHARGES recorded from pre- or postganglionic sympathetic nerve bundles usually are synchronized into bursts that are locked in a 1:1 relation to the cardiac cycle (3-5 cycle/s periodicity). The cardiac rhythm within sympathetic nervous discharge (SND) is generally assumed to result directly from the waxing and waning of baroreceptor nerve activity associated respectively with systole and diastole (1, 4, 17, 18). However, this view has been challenged by Taylor and Gebber (24) and Gebber et al. (10). These investigators noted that bilateral section of the carotid sinus, aortic depressor, and vagus nerves uncoupled the phase relations between splanchnic or renal SND and the cardiac cycle in the cat, but the 3-5 cycle/s periodicity persisted. That is, synchronization of SND into ≈200-ms slow waves was not prevented by baroreceptor denervation. It was also demonstrated that a complete oscillation of SND was aborted by a single shock delivered to the baroreceptor reflex arc early in the cardiac cycle. These observations led Taylor and Gebber to suggest that the 3-5 cycle/s periodic component of SND is representative of a sympathetic rhythm of central origin that normally is entrained to the cardiac cycle by the baroreceptor reflexes. In a subsequent study, McCall and Gebber (21) provided evidence that the 3-5 cycle/s periodicity of SND reflects the fundamental organization of the brainstem vasomotor system.

The present investigation was designed to test further the hypothesis that the brainstem vasomotor system is inherently capable of synchronizing the discharge of groups of sympathetic neurons. It was reasoned that it should be possible to reset the phase relations between baroreceptor and sympathetic nerve discharge if the 3-5 cycle/s periodicity is representative of a vasomotor rhythm of central origin. Resetting was accomplished by slowing heart rate with vagus nerve stimulation. In addition, the time course of sympathoinhibition of baroreceptor origin associated with the cardiac cycle was revealed with the technique of computer summation.

METHODS

Twenty-four cats weighing between 2.0 and 4.0 kg were anesthetized by the intraperitoneal injection of a mixture of sodium diallylbarbiturate (70 mg/kg), urethane (280 mg/kg), and monoethylurea (280 mg/kg). Rectal temperature was maintained between 36 and 38°C with a heat lamp. The animals were immobilized with decamethonium bromide (0.5 mg/kg iv) and artificially respired. Supplemental doses of decamethonium were administered as required to prevent somatomotor movement. Pneumothoracotomy was routinely performed. Blood pressure was monitored from the lumbar aorta (via a femoral catheter) and displayed on a Grass model 7B polygraph.

Isolation of nerves. The surgical approaches employed have been described in detail in previous reports from this laboratory (11, 23, 24). The external carotid postganglionic sympathetic branch of the superior cervical ganglion, carotid sinus, aortic depressor, and vagus nerves were exposed from a ventral aspect after reflection of a portion of the trachea and esophagus into the mouth. The vagus and aortic depressor nerves were sectioned bilaterally in all experiments. The distal end of the right cervical vagus nerve was stimulated with square-wave pulses (10 V, 0.5 ms) passed from a Grass S88 stimulator through an isolation unit to bipolar platinum electrodes.

The left preganglionic greater splanchnic nerve and postganglionic renal nerves were exposed via a retroperitoneal approach. The splanchnic nerve was identified in
the area of the costovertebral triangle and cut at its entrance into the celiac ganglion. One of the renal nerves was traced to and sectioned near its entrance into the kidney.

Nerve recording and data analysis. Discharges were recorded monophasically under oil with bipolar platinum electrodes from the carotid sinus, preganglionic splanchnic, and postganglionic renal and external carotid nerves. Capacity-coupled preamplification with a wide band pass (0.1–1,000 Hz) allowed the synchronized discharge of groups of afferent baroreceptor or efferent sympathetic fibers to be viewed in the form of a slow wave [i.e., an envelope of spikes (4, 21, 24)]. Recordings were made from only one of the three efferent sympathetic nerves in any particular experiment. The relationships between SND and the cardiac cycle were essentially identical independent of the efferent nerve employed. Consequently, the specific site of recording of efferent discharge is referred to in the figure legends rather than in the text.

Recorded nerve activity was stored on magnetic tape and simultaneously displayed on a storage oscilloscope and the polygraph. As previously described (24), the time relations between spontaneously occurring nerve discharge, whether afferent or efferent, and the cardiac cycle were analyzed by computer summation (Nicolet model 1070). The sweep of the computer was initiated by a timing pulse from a logic-divider trigger circuit that was derived from the R wave of the electrocardiogram (ECG). The memory content of the computer was displayed in analog or digital form on an oscilloscope.

Statistical methods. Statistical analysis was performed with the Student t test for paired data. P values of <0.05 were considered to indicate statistical significance. Values are expressed as means ± SE.

RESULTS

Effect of stimulation of vagus on phase relations between SND and cardiac cycle. The effect of slowing heart rate on the phase relations between the arterial pulse and spontaneously occurring SND is shown in Fig. 1. Changes in heart rate were produced by stimulation of the distal end of the sectioned right vagus nerve in cats in which both aortic depressor nerves and the left vagus also were cut. At control heart rate (panel A), SND was synchronized into slow waves that were locked in a 1:1 relation to the cardiac cycle. One-to-one locking was maintained when the vagus was stimulated at frequencies (2–5 Hz) that progressively lowered heart rate to about 2 beats/s (panels B, C). It became evident, however, that the phase relations between SND and the cardiac cycle were dependent on heart rate. This is most clearly seen by comparing panels A and C. The point of maximum SND was shifted from the end of the first third of diastole to near peak systole when heart rate was lowered. With few exceptions, the 1:1 relationship between the slow wave of SND and the cardiac cycle was disrupted when heart rate was decreased below 2 beats/s by higher frequency (10–20 Hz) stimulation of the vagus (panels D, E, F). That is, the ratio of slow waves per cardiac cycle was greater than 1 at heart rates below 2 beats/s. Slow waves of SND with durations approximating 200 ms and 100 ms appeared under these conditions. The ≈200 ms slow wave appeared similar in form to those bursts that were locked in a 1:1 relation to the

![Fig. 1. Oscillographic tracings depicting phase relations between arterial pulse (top) and spontaneously occurring external carotid postganglionic SND (bottom). Negativity is upward in this and all subsequent figures. A: control. B–F: during stimulation of distal end of right vagus nerve. B, 3 Hz; C, 5 Hz; D, 10 Hz; E, 15 Hz; F, 20 Hz. G–I: after bilateral section of carotid sinus nerves (vagi and aortic depressor nerves previously cut). Changes in mean blood pressure are not depicted in records. Blood pressure was 150 mm Hg before (A) and 185 mmHg after (G) section of carotid sinus nerves. Horizontal calibration, 200 ms; vertical calibration, 20 μV.](http://ajplegacy.physiology.org/Downloadedfrom)
cardiac cycle at higher heart rates. The 100-ms wave form (10-cycle/s periodicity) has been previously reported in the cardiac (16), cervical (14), renal (21), and splanchnic (3, 4, 14, 15) nerves of the cat. Synchronization at the spinal level is responsible for the 100-ms slow wave of SND (21).

Although the phase relations between SND and the cardiac cycle were unlocked by baroreceptor denervation, synchronization of SND into slow waves persisted (panels C, H. I). The records of SND after bilateral section of the carotid sinus nerves are similar to those observed before baroreceptor denervation at heart rates below 2 beats/s. The ~200-ms slow wave was generated aperiodically at frequencies ranging from 3 to 5 cycles/s. Occasional 100-ms slow waves were observed.

**Phase relations with ratio of slow waves per cardiac cycle maintained at 1.** Computer summation was employed to quantify the shifts in the phase relations between SND and the cardiac cycle that accompanied cardiac slowing. Figure 2 is representative of the results obtained when the ratio of slow waves of SND per cardiac cycle (as monitored on the storage oscilloscope or polygraph) was maintained at 1 during stimulation of the vagus. Each trace is the sum of 64 R wave-triggered trials. The point of maximum SND was shifted from early diastole (panel A) to near peak systole (panel B) when heart rate was slowed from 4.4 beats/s to 3.5 beats/s. Further slowing to 2.4 beats/s shifted the point of maximum SND into the late diastolic phase of the preceding cardiac cycle (panel C). Increased variation of the interval between heartbeats during vagus stimulation accounted for the small reduction in peak amplitude of the second computer-summed arterial pulse in panel C.

The results of 13 experiments in which the right vagus was stimulated at frequencies that decreased heart rate while maintaining the ratio of slow waves of SND per cardiac cycle at 1 are summarized in Table 1. When required, phenylephrine hydrochloride (5-10 µg/min iv) was infused to maintain arterial blood pressure near 150 mmHg, a level at which SND was tightly locked to the cardiac cycle. For reasons that are discussed subsequently, measurements were made from the computer-summed slow wave of SND, the peak of which was closest to the systolic phase of the second arterial pulse. The parameters compared before and during vagus stimulation are depicted in Fig. 3. The interval between the R wave trigger and the peak of the second systole (R-Pk SYS) was increased 52% when heart rate was lowered from 3.6 to 2.2 beats/s. Concurrently, the interval between the R wave trigger and the point of maximum SND in the slow wave closest to the systolic phase of the second arterial pulse (R-Pk SND) was increased 19%. The changes in the R-Pk SYS and R-Pk SND intervals were significantly different from each other. This observation attests to a shift in the phase relations between SND and the cardiac cycle. Peak-to-peak amplitude of the slow wave of SND was significantly increased during stimulation of the vagus. This observation is in accord with the inverse relationship between SND per beat and pulse rate reported by Baum and Shropshire (2). One-half amplitude width of the negative phase of the slow wave (treated as sinusoidal in character) was not significantly changed when heart rate was slowed. This observation suggests that the basic 200-ms wave form within SND was not altered even though the total duration of the slow wave (measured at its base) increased during cardiac slowing.

**Phase relations with ratio of slow waves per cardiac cycle greater than 1.** As was shown in Fig. 1 (panels D, E, F), the 1:1 relationship between the slow wave of SND and the cardiac cycle was disrupted (i.e., ratio of slow waves per cardiac cycle greater than 1) when heart rate was decreased below 2 beats/s by vagus stimulation. Computer-summed records depicting the relations between SND and the arterial pulse under these conditions are shown in Fig. 4. A period of R wave-locked positivity followed by rebound negativity was evident during vagus stimulation. Positive potentials result from intervals of decreased SND locked to the R wave. Thus, the period of baroreceptor-induced sympathoinhibition associated with the cardiac cycle was unmasked.

![FIG. 2. Shifts in phase relations between arterial pulse (top) and slow wave of external carotid postganglionic SND (bottom) produced by vagus nerve stimulation (ratio of slow waves per cardiac cycle maintained at 1). Traces are sum of 64 R wave-triggered trials. A: control. B: during vagus stimulation (3 Hz). C: vagus stimulation (5 Hz). Mean blood pressure was 163 mmHg in A, 160 mmHg in B and 187 mmHg in C. Horizontal calibration, 500 ms; vertical calibration, 133 µV.](http://ajplegacy.physiology.org/ Downloaded from http://ajplegacy.physiology.org/ by 10.220-22.277 on May 24, 2017)
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When the phase relations between the slow wave of SND and the arterial pulse was disrupted. The onset of positivity most often appeared in early diastole (Fig. 4, IB). However, in some experiments, an additional and earlier component of positivity was present (Fig. 4, IIB). The onset of the early phase of positivity appeared near the beginning of systole. The interval between the R wave and the onset of the early positivity was 88±4 ms in three experiments. The duration of the early positive potential could not be measured accurately since this wave form never was observed independently and always overlapped with the late phase of positivity. The interval between the R wave and the onset of the late positive potential was 181±13 ms in eight experiments. Strikingly, the shape and duration (199±15 ms) of the late positive potential, which was unmasked during vagus stimulation, approximated those for the spontaneously occurring slow wave of SND derived by computer summation in the absence of vagus nerve stimulation. One such example is presented in Fig. 5.

Additional evidence for an early component of baroreceptor-induced sympathoinhibition was obtained when mean blood pressure was raised above 180 mmHg by the intravenous infusion of phenylephrine (10–30 μg/min). One of the three experiments performed is illustrated in Fig. 6. The rise in blood pressure produced by phenylephrine had little effect on heart rate or the phase relations between SND and the cardiac cycle. However, a prominent inflection on the rising phase of the slow wave was observed near the beginning of systole. The inflection began 92 ms after the R wave trigger in this experiment.

Phase relations between baroreceptor and sympathetic nerve activity. The phase relations between SND and carotid sinus nerve activity were studied for three reasons. First, it was important to demonstrate directly resetting of the phase relations between baroreceptor and sympathetic nerve discharge. Second, the interval between the R wave and the start of the pulse synchronou

uous component of carotid sinus nerve discharge was required to determine the onset latencies of the early and late phases of baroreceptor-induced sympathoinhibition. Third, the question arose whether the increase (19%) of the R-Pk SND interval (Table 1) observed during slowing of the heart rate was related to a change in the character of the pulse-synchronous component of carotid sinus nerve activity.

FIG. 4. Relationships between external carotid (I) and splanchnic (II) SND and arterial pulse when ratio of slow waves per cardiac cycle was greater than 1 during vagus nerve stimulation. Traces are sum of 64 R wave-triggered trials. Records in I and II are from 2 different cats. A: control. B: during vagus stimulation (10 Hz). Mean blood pressure was 155 mmHg in IA and 123 mmHg in IB. Blood pressure was 133 mmHg in IA and 115 mmHg in IIB. Horizontal calibration, 500 ms; vertical calibration, 67 μV for records in I and 267 μV for records in II.

FIG. 5. Comparison of shapes of R wave-locked (a) slow wave of external carotid SND and (b) late positive potential recorded from same cat. A: superimposition of 1 slow wave of SND and inverted positive potential. Traces were derived from B and C. B: trace of SND is sum of 64 R wave-triggered trials in absence of vagus stimulation. C: sum of 64 R wave-triggered trials during vagus stimulation (20 Hz). Horizontal calibration, 500 ms; vertical calibration, 287 μV.

FIG. 6. Early component of baroreceptor-induced sympathoinhibition. Traces of arterial pulse (top) and external carotid SND (bottom) are sum of 32 R wave-triggered trials. A: control; mean blood pressure was 147 mmHg. B: during infusion of phenylephrine (20 μg/min iv); mean blood pressure was 183 mmHg. Note inflection on rising phase of slow wave of SND. Horizontal calibration, 250 ms; vertical calibration, 133 μV for A and 67 μV for B.
Discharges were recorded from the peripheral end of the cut right carotid sinus nerve in cats in which the vagus and aortic depressor nerves were bilaterally sectioned. The contralateral carotid sinus nerve was left intact in an attempt to preserve locking between sympathetic and baroreceptor nerve discharge. The characteristics of pulse-synchronous carotid sinus nerve activity recorded from the same cat with two different preamplifier band passes are shown in Fig. 7. With the band pass set at 30–1,000 Hz, carotid sinus nerve discharge appeared as a burst of high-frequency spikes (panel A). The pulse-synchronous component of carotid sinus nerve discharge was viewed primarily as a slow wave (i.e., envelope of spikes) when the preamplifier band pass was set at 0.1–1,000 Hz (panel B). Note that the slow wave accurately depicts the period of high-frequency spiking. The onset of carotid sinus nerve discharge somewhat preceded the start of the systolic phase of the lumbar aortic pulse. This observation presumably was the result of a difference in the time of conduction of the pulse wave from the heart to the carotid sinus and lumbar aorta.

Carotid sinus nerve discharge was analyzed by computer summation with the wider preamplifier band pass. Sympathetic nervous discharge and baroreceptor nerve activity were locked in a 1:1 relation in four of the eight experiments performed. The results obtained in two of these experiments are presented in Fig. 8. The point of maximum SND occurred near the start of the falling phase of carotid sinus nerve activity when heart rate was 3.1 beats/s (panel IA). Shifts in the phase relations between baroreceptor and sympathetic nerve activity occurred when heart rate was slowed by vagus nerve stimulation (panels IB, IC). Maximum SND was reached before the start of the pulse-synchronous component of baroreceptor nerve discharge when heart rate was 1.7 beats/s (panel IC). The ratio of slow waves per cardiac cycle was maintained at 1 during vagus stimulation in this experiment. The computer-summed trace of SND was characterized by a R wave-locked complex of positivity followed by rebound negativity when cardiac slowing was accompanied by disruption of the 1:1 relationship between bursts of sympathetic and baroreceptor nerve discharge (Fig. 8, II). The onset of sympathoinhibition (positive potential) occurred 95 ms after the beginning of the rising phase of the pulse synchronous component of carotid sinus nerve discharge (panel II). The earlier phase of inhibition was not observed in experiments in which only one carotid sinus nerve remained intact.

A comparison of the characteristics of the pulse-synchronous component of carotid sinus nerve discharge before and during vagus nerve stimulation is presented in Table 2. Measurements were made from the wave form associated with the R wave trigger. The onset latency of the discharge was about 70 ms. This value lies

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<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>Vagus Stimulation</th>
<th>% of Control</th>
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<tbody>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>149 ± 4</td>
<td>139 ± 7</td>
<td>93.0 ± 2.5*</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>57 ± 4</td>
<td>74 ± 6</td>
<td>131.8 ± 7.8*</td>
</tr>
<tr>
<td>Heart rate, beats/s</td>
<td>3.62 ± 0.17</td>
<td>2.23 ± 0.09</td>
<td>62.8 ± 2.5*</td>
</tr>
<tr>
<td>R-Pk SYS interval, ms</td>
<td>424 ± 18</td>
<td>639 ± 24</td>
<td>152.1 ± 5.6*</td>
</tr>
<tr>
<td>R-Pk SND interval, ms</td>
<td>433 ± 17</td>
<td>513 ± 13</td>
<td>119.2 ± 2.1**</td>
</tr>
<tr>
<td>Slow wave amplitude, μV</td>
<td>277 ± 41</td>
<td>388 ± 70</td>
<td>142.0 ± 14.9*</td>
</tr>
<tr>
<td>Slow wave, 1/2 amplitude width, ms</td>
<td>107 ± 7</td>
<td>112 ± 6</td>
<td>105.3 ± 2.9</td>
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</table>

Values are means ± SE for 13 experiments. Ratio of slow waves per cardiac cycle was maintained at 1 during vagus stimulation (10 V, 0.5 ms, 2–5 Hz). *Statistical significance ($P < 0.05$) on basis of paired comparison. **Significantly different ($P < 0.05$) from change in R-Pk SYS interval.

![FIG. 7. Oscillographic tracings depicting characteristics of carotid sinus nerve discharge recorded with preamplifier band-pass settings of 30–1,000 Hz (A) and 0.1–1,000 Hz (B). Top traces: arterial pulse. Bottom traces: carotid sinus nerve discharge. Mean blood pressure was 145 mmHg.](http://ajplegacy.physiology.org/)

![FIG. 7. Oscillographic tracings depicting characteristics of carotid sinus nerve discharge recorded with preamplifier band-pass settings of 30–1,000 Hz (A) and 0.1–1,000 Hz (B). Top traces: arterial pulse. Bottom traces: carotid sinus nerve discharge. Mean blood pressure was 145 mmHg.](http://ajplegacy.physiology.org/)

![FIG. 8. Phase relations between pulse-synchronous component of carotid sinus nerve discharge and renal (I) or external carotid (III) SND. Records in I and II are from 2 different cats and represent sum of 64 R wave-triggered trials. Top tracings: arterial pulse. Middle tracings: carotid sinus nerve discharge. Bottom tracings: SND. IA: control; mean blood pressure was 145 mmHg. IB: vagus stimulation (3 Hz); blood pressure was 140 mmHg. IC: vagus stimulation (5 Hz); blood pressure was 140 mmHg. Ratio of slow waves of SND per cardiac cycle was maintained at 1 during vagus stimulation in experiment I. IIA: control; blood pressure was 128 mmHg. IIIA: vagus stimulation (20 Hz); blood pressure was 110 mmHg. Ratio of slow waves per cardiac cycle was greater than 1 during vagus stimulation in experiment II. Horizontal calibration, 500 ms; vertical calibration, 534 μV for records in I and 237 μV for records in II.](http://ajplegacy.physiology.org/)
TABLE 2. Effect of vagus stimulation on pulse-synchronous component of carotid sinus nerve discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control</th>
<th>Vagus Stimulation</th>
<th>% of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>153 ± 6</td>
<td>132 ± 7</td>
<td>86.2 ± 3.6*</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>49 ± 5</td>
<td>68 ± 8</td>
<td>146.9 ± 19.7*</td>
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<tr>
<td>Heart rate, beats/s</td>
<td>3.49 ± 0.18</td>
<td>2.04 ± 0.07</td>
<td>59.3 ± 3.4*</td>
</tr>
<tr>
<td>Discharge, onset latency, ms</td>
<td>69 ± 3</td>
<td>71 ± 2</td>
<td>103.7 ± 2.4</td>
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<tr>
<td>Discharge, amplitude, μV</td>
<td>263 ± 74</td>
<td>238 ± 67</td>
<td>108.4 ± 18.9</td>
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<tr>
<td>Discharge, 1/2 amplitude width, ms</td>
<td>77 ± 12</td>
<td>124 ± 14</td>
<td>175.4 ± 19.2*</td>
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</table>

Values are mean ± SE for 8 experiments. *Statistical significance (P < 0.05) on basis of paired comparison.

between those reported for the cat by Gabriel and Seller (9) and Irisawa and Ninomiya (19). One-half amplitude width of the computer-summed slow wave (treated as pulsatile rather than sinusoidal in character) was significantly increased, whereas the amplitude of carotid sinus nerve discharge was not changed during stimulation of the vagus. These observations may be related to the combination of decreased mean arterial pressure and increased pulse pressure with cardiac slowing.

DISCUSSION

The 1:1 relation between bursts of SND and the cardiac cycle is generally considered to be a simple consequence of the baroreceptor reflexes (1, 4, 17, 18). It is supposed that increased baroreceptor nerve discharge during systole causes a delayed inhibition of SND and that the fall in pressure from peak systole results in a delayed removal of inhibition. As summarized by Cohen and Gootman (4), the delay between afferent and efferent activity changes is thought to be dependent on: a) temporal dispersion of discharge from different baroreceptors at the same vascular site (7, 12); b) temporal dispersion of baroreceptor discharge from different vascular sites (19); c) delay time within the brainstem vasomotor system (unknown); and d) delay from the brainstem centers to the peripheral sympathetic fibers, which minimally is about 40 ms in the splanchnic nerve (13), 44 ms in the renal nerve (5), and 50 ms in the external carotid nerve (11). The results of the present investigation, however, indicate that the 1:1 relation between bursts of activity in baroreceptor and sympathetic nerves cannot be explained solely on the basis of these factors.

Of the utmost importance was the observation that the phase relations between the arterial pulse and SND could be reset dramatically by slowing the heart rate. Whereas the point of maximum SND occurred in early or middiastole at heart rates between 3 and 4 beats/s, maximum activity was shifted backwards to peak systole and then into late diastole of the preceding cardiac cycle when heart rate was progressively lowered to 2 beats/s. Comparable shifts were seen in the phase relations between sympathetic and carotid sinus nerve discharge. These data suggest that decay of SND (i.e., falling phase of slow wave) is not the direct consequence of delayed inhibition of baroreceptor reflex origin. Strong support for this contention was offered in Fig. 8. The falling phase of the slow wave of SND was initiated before the onset of the pulse synchronous component of carotid sinus nerve activity at heart rates near 2 beats/s.

It is more reasonable to explain 1:1 locking of the slow wave of SND to the cardiac cycle on the basis of entrainment by the baroreceptor reflexes of a sympathetic rhythm of central origin. In this regard, Taylor and Gebber (24) and Gebber et al. (10) demonstrated that while the phase relations between SND and the cardiac cycle were unlocked by baroreceptor denervation the 3-5 cycle/s periodicity persisted. Furthermore, one complete slow wave of SND was aborted by a single shock delivered to the baroreceptor reflex arc during a time span that accounted for less than 1% of the duration of the cardiac cycle. These data led to the conclusion that the 3-5 cycle/s periodic component of SND is representative of a sympathetic rhythm of brainstem rather than of baroreceptor reflex origin. It was further suggested that the baroreceptor reflexes entrained the centrally generated slow wave in a 1:1 relation to the cardiac cycle in order to control the periodicity of SND. Direct evidence for this contention was provided in the present investigation. The ratio of slow waves per cardiac cycle was maintained at 1 between heart rates of 2 and 4 beats/s. However, the baroreceptor reflexes lost control over the periodicity of SND at lower heart rates. The =200-ms slow waves were generated aperiodically at frequencies ranging from 3 to 5 cycles/s when heart rate was lowered to less than 2 beats/s.

Entrainment of the centrally generated slow wave of SND to the cardiac cycle by the baroreceptor reflexes can be explained by inhibitory phasing. The waxing and waning of baroreceptor nervous discharge is imperative to the inhibitory-phasing hypothesis. The brainstem network responsible for generation of the slow wave of SND is triggered when inhibition of baroreceptor origin drops below some critical level during each cardiac cycle. That is, the decay of brainstem inhibition (which begins at the end of the systole that precedes the onset of slow wave) acts to trigger the pontomedullary network responsible for the synchronized burst of SND. This explanation is quite different from that relating the decay of SND to the development of inhibition during the systole that follows the onset of the slow wave. Shifts in the phase relations between sympathetic and baroreceptor nervous discharge are easily explained by the inhibitory-phasing hypothesis. Lengthening of the interval between heartbeats by vagus stimulation would result in a shift of the peak of the slow wave of SND from the early diastolic phase of one cardiac cycle to the late diastolic phase of the preceding cardiac cycle.

The R-Pk SND interval was increased during cardiac slowing produced by stimulation of the vagus (Table 1). This change may be related to the concurrent increase in the duration (one-half amplitude width) of the pulse-synchronous component of carotid sinus nerve dis...
charge. That is, generation of the slow wave may have been postponed as the result of delayed decay of inhibition of baroreceptor reflex origin. Increased pulse pressure during cardiac slowing presumably led to the change in duration of carotid sinus nerve discharge.

Taylor and Gebber (24) have provided evidence for the existence of two distinct components of baroreceptor-induced sympathoinhibition. Inhibition of spontaneously occurring splanchnic or renal nerve discharge produced by 5-ms trains of three pulses applied to the carotid sinus nerve or to the medullary depressor region was viewed as a computer-summed positive potential. Positivity produced by stimulation of the baroreceptor reflex arc contained an early and a late component. Importantly, discharges elicited in the splanchnic nerve by stimulation of descending spinal pressor tracts were inhibited during the time course of the early but not the late positive potential. This observation led Taylor and Gebber to conclude that the early positive potential monitored sympathoinhibition exerted at a spinal level while the late positive potential monitored inhibition in the brainstem.

In the present study, the period of sympathoinhibition associated with the pulse-synchronous component of carotid sinus nerve discharge was revealed in the form of computer-summed positivity at heart rates below 2 beats/s. The 1:1 relationship between the slow wave of SND and the cardiac cycle was disrupted under these conditions. Subtraction of the interval (70 ms) between the R wave and the onset of carotid sinus nerve discharge from those between the R wave and the early and late phases of positivity yielded mean values of 18 and 111 ms. These values are reasonably close to those reported by Taylor and Gebber (24) and Gootman and Cohen (13) for the onset latencies of the early and late positive potentials elicited by electrical stimulation of the baroreceptor reflex arc. The values (94–260 ms) reported by others (6, 8, 17, 20, 22) for the delay between the start of baroreceptor nerve activity and inhibition of SND are considerably greater than that reported (18 ms) for the onset latency of the early positive potential. The failure of previous investigators to observe the early phase of baroreceptor-induced sympathoinhibition probably is related to two factors. First, computer summation was not utilized to analyze the time course of inhibition of spontaneously occurring SND. Second, attempts to disrupt the 1:1 relationship between the slow wave of SND and the cardiac cycle with vagus stimulation were not made in these earlier studies. With regard to these points, an inflection on the rising phase of the computer-summed slow wave (Fig. 6) was the only sign of early inhibition observed at control heart rate. Furthermore, the inflection was present only when systemic blood pressure was raised above 180 mmHg with phenylephrine infusion.

The roles played by the two components of baroreceptor-induced inhibition in the control of SND should be considered. Taylor and Gebber (24) reported that the shape of the late positive potential elicited by electrical stimulation of the baroreceptor reflex arc was essentially identical to that of the computer-summed spontaneously occurring slow wave of SND. The same relationship was found in the present study when the shape of the positive potential locked to the R wave was compared with that of the spontaneously occurring slow wave (Fig. 5). These observations most likely are explained by the ability of a single shock applied to the baroreceptor reflex arc early in the cardiac cycle to abort one complete oscillation of SND (24). On this basis, the R wave-locked late positive potential would monitor, in an indirect way, the ability of the baroreceptor reflexes to entrain the slow wave of SND to the cardiac cycle.

The late positive potential unmasked during cardiac slowing usually began in early diastole. Yet, the sinusoidal character of the falling phase of the slow wave was not disrupted even though peak SND fell in early diastole at control heart rate. This observation can be related to the findings of Taylor and Gebber (24). They noted that electrical stimuli applied to the baroreceptor reflex arc soon after (40 ms) the beginning of the slow wave failed to alter its development. This result led to the suggestion that brainstem inhibition of baroreceptor origin was exerted high in the nerve network responsible for synchronization of SND into 200-ms slow waves.

At high systemic arterial pressure and in the absence of cardiac slowing (Fig. 6), a prominent inflection on the rising phase of the slow wave occurred at a time coincident with the onset latency of the early positive potential unmasked during stimulation of the vagus. Thus, the wave of activity synchronized in pontomedullary networks and entrained to the cardiac cycle by the brainstem component of inhibition is further influenced at a spinal level by the baroreceptor reflexes. The spinal component of baroreceptor-induced sympathoinhibition undoubtedly functions to control the amplitude and shape of the slow wave. Further study is necessary, however, to determine the time course of spinal inhibition during each cardiac cycle as well as the relationship between the degree of activation of this system and carotid sinus pressure. Such experiments might provide the basis for the changes in contour (e.g., broadened base) and amplitude of the slow wave of SND observed during cardiac slowing.

It is apparent from the present investigation that baroreceptor reflex control of SND is considerably more complicated than previously supposed. Each slow wave of SND is affected by baroreceptor nervous discharge occurring over two cardiac cycles at heart rates between 3 and 4 beats/s. The formation of the slow wave is triggered when brainstem inhibition occurring during the first cardiac cycle decays to a critical level. Spinal inhibition associated with baroreceptor nerve discharge in the second cardiac cycle influences the number and sequence of activation of preganglionic neurons by the wave of synchronized activity descending from the brainstem.

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