Vagal Afferent Inhibition of Spinothalamic Cell Responses to Sympathetic Afferents and Bradykinin in the Monkey

W. Steve Ammons, Robert W. Blair, and Robert D. Foreman
From the Department of Physiology and Biophysics, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

SUMMARY. Effects of stimulating the left thoracic vagus nerve on the responses of spinothalamic neurons to electrical stimulation of cardiopulmonary sympathetic afferent fibers and to intracardiac injections of bradykinin were determined. Experiments were performed on 39 monkeys (Macaca fascicularis) tranquilized with ketamine and anesthetized with a-chloralose. The 30 spinothalamic cells studied had the following characteristics. They were excited by manipulation of their somatic receptive fields, were excited by electrical stimulation of cardiopulmonary sympathetic afferent fibers, and exhibited viscerosomatic convergence. Responses of 15 of 19 cells to sympathetic afferent test stimuli were inhibited by conditioning stimuli applied to left thoracic vagus nerve. A conditioning-test interval of 40-50 msec resulted in maximal inhibition of responses to both Aδ and C fiber sympathetic afferents. A long time course of inhibition was present to at least a conditioning-test interval of 200 msec. Left thoracic vagus nerve stimulation inhibited 14 of 14 cells responding to intracardiac injection of bradykinin. Entrainment of activity of five cells to the cardiac cycle occurred in response to bradykinin. In each case, left thoracic vagus nerve stimulation, in addition to reducing frequency of cell discharge, disrupted the cardiac related pattern of cell activity. Bilateral cervical vagotomy abolished all inhibitory effects of left thoracic vagus nerve stimulation. These results demonstrate that vagal afferents may participate in processing of information related to cardiac pain.

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CARDIAC PAIN associated with angina pectoris or myocardial infarction is the result of neural activity carried by sympathetic afferent fibers that enter the spinal cord via the T1-T4 rami communicantes (White et al., 1933; White, 1957). Within the spinal cord, sympathetic afferent activity may activate segmental circuits leading to cardiocardiac reflexes (Malliani et al., 1969). For anginal pain to occur, sympathetic afferent activity must also activate cells in the spinal cord which transmit information to regions of the brain involved in perception of pain. Recent studies from our laboratory showed that electrical stimulation of cardiopulmonary sympathetic afferent fibers excites spinothalamic tract (ST) neurons in the upper thoracic spinal cord (Blair et al., 1981). Bradykinin—a potent algesic agent that activates sympathetic afferents (Baker et al., 1980; Lombardi et al., 1981), produces pseudoadverse responses (Guzman et al., 1962), and appears in the coronary sinus of the ischemic heart (Kimura et al., 1973)—also activates ST neurons (Blair et al., 1982). All ST neurons which responded to bradykinin or electrical stimulation of sympathetic afferents were also activated by somatic stimuli (Blair et al., 1981, 1982). Convergence of cardiac sympathetic afferents with somatic afferents may explain why a large percentage of patients with myocardial ischemia have pain referred to the chest wall or arms (Scherf and Boyd, 1958). Taken together, these studies suggest that painful sensations of cardiac origin are due to activation of neural circuits which include upper thoracic ST neurons and sympathetic afferent fibers.

Vagal afferents, as well as sympathetic afferents, influence the activity of ST neurons. We have shown that electrical stimulation of cardiopulmonary vagal afferents inhibits the background activity of ST neurons as well as their responses to somatic stimuli (Ammons et al., 1983). Thus, vagal afferent information, presumably by way of bulbospinal networks, converges with sympathetic afferent information onto the same ST neurons. This finding suggests that—in addition to their known roles in mediating associated hypotension, bradycardia, and decreased sympathetic nerve activity (Kezdi et al., 1974; Felder and Thames, 1979; Thames and Abbott, 1979)—vagal efferents which are activated by myocardial ischemia may also play a role in transmission of information related to cardiac pain. To provide evidence for a role of vagal afferents in modulation of cardiac pain, it is necessary to determine whether stimulation of the vagus nerve alters the ST cell response to sympathetic afferent stimuli. In our earlier study, we tested for vagal effects on somatic, but not visceral, stimuli, and it is possible that the inhibition we observed in that study was a specific effect exerted only on responses to somatic afferents. Thus, the present study was carried out to provide specific evidence for a role of the vagus
nerve in processing of information concerning noxious cardiac events. We examined the effects of electrical stimulation of the left thoracic vagus nerve on responses of ST neurons to electrical stimulation of sympathetic afferents and to intracardiac injections of bradykinin.

Methods

Experiments were performed on 39 monkeys (Macaca fascicularis) weighing between 2.7 and 6.7 kg. They were tranquilized with ketamine (10–20 mg/kg) and anesthetized with α-chloralose (80 mg/kg). During the recording procedure, a constant infusion of sodium pentobarbital (2–4 mg/kg per hour) was used to maintain the anesthetic level, and either gallamine triethiodide (1–2 mg/kg per hour) or pancuronium bromide (0.15 μg/kg per hour) was used to maintain muscle paralysis.

The surgical procedure has been described in detail elsewhere (Blair et al., 1981, 1982). Briefly, artificial ventilation was provided, respiratory CO2 was maintained between 3.5% and 4.5%, and temperature was maintained at 37 ± 1°C. A catheter was placed in a femoral artery to measure arterial pressure. Throughout the experimental procedure, blood pressure, heart rate, and the ECG were recorded. Catheters were also placed in a femoral vein for fluid infusion and in the left atrial appendage for injection of bradykinin.

A bipolar electrode was placed on the cardiopulmonary sympathetic fibers, as previously described (Blair et al., 1981, 1982). An additional bipolar electrode was placed on the left thoracic vagus nerve just cephalad to the aortic arch. In two experiments, an electrode was also placed on the cardiac branch of the vagus. The electrodes were held in place with low melting point wax to prevent the nerves from drying out. Ligatures were placed around both vagi in the neck so that bilateral vagotomy could be performed at a later time. In two experiments, vagal cooling coils were placed around each cervical vagus nerve in order to perform vagal cold block. At this point, the animals were mounted in a stereotaxic frame. A bipolar stainless steel electrode was positioned in the right ventral posterior lateral nucleus (VPL) of the thalamus with the aid of evoked responses of the nucleus to somatic manipulation of the left forelimb and chest. In any one experiment, three segments of the spinal cord were exposed by laminectomy, although the three segments chosen for study varied from experiment to experiment, ranging from T1 to T3.

The protocol was as follows. Gray matter on the left side of the spinal cord was searched, with tungsten or carbon-tipped glass microelectrodes, for cells which were antidromically activated by stimulating VPL (100 μsec duration, 2 mA, 10 Hz). Cell activity was recorded and displayed by means of standard techniques. All of the cells studied met the standard criteria for antidromic activation (Trevino et al., 1973).

Once a ST neuron was identified, the type of sympathetic afferent fiber input it received and its somatic receptive field were determined. Sympathetic afferent input was analyzed by constructing post-stimulus histograms. Stimulus intensities varied from 0.7 to 33 V and 100- to 500-μsec duration. One or more response peaks occurred in these histograms. Minimum afferent conduction velocity (Foreman et al., 1975) was calculated and voltage thresholds determined for each peak. Each cell had either an Aδ response peak or Aδ and C fiber peaks. C fibers were judged to be activated when the later peak had a minimum afferent conduction velocity of 2 m/sec or less, and a threshold greater than the first peak. All cells in this study responded to activation of somatic and sympathetic afferent fibers, and thus received visceral-somatic convergent inputs.

All cells were initially tested for responsiveness to left thoracic vagus nerve (LTV) stimulation. Cells with little or no background activity were tested for responses to LTV stimulation during activation elicited by a somatic stimulus such as pinching the skin. Vagal stimuli 2 msec in duration were delivered at a frequency of 20 Hz. The stimulus intensity ranged from 2 to 35 V and was chosen in order to obtain a near maximal response without appearance of the stimulus artifact in the window of the discriminator. Cells inhibited by LTV stimulation were tested for vagal inhibition of responses to sympathetic afferent fiber stimulation, intracardiac injection of bradykinin, or both.

The conditioning-test (CT) technique was used to demonstrate vagal inhibition of cell responses to sympathetic afferent stimulation. Initially, a post-stimulus histogram of the cell's response to the sympathetic afferent test stimulus, only, was constructed as described above. Next, another post-stimulus histogram was constructed when the conditioning stimulus was applied to LTV 20 to 200 msec before the sympathetic afferent test stimulus. The vagal conditioning stimulus consisted of a 10-msec train of stimuli (100 μsec, 10–33 V, 333 Hz). The period between the conditioning and test stimuli is called the CT interval. Histograms were generated for several different CT intervals for each cell. Periodically during the procedure, control histograms of the test response alone were repeated. The number of spikes elicited by the test stimulus was determined from the histograms for each CT interval. These values were expressed as a percentage of the number of spikes resulting from the test stimulus alone and were plotted (Fig. 1).

Bradykinin (in a dose of 2 μg/kg) was injected into the left atrium. In an earlier study, we demonstrated that this route of bradykinin injection activates primarily cardiac receptors and not receptors outside the heart (Blair et al., 1982). If the cell increased its discharge rate, LTV was stimulated at a point at which cell activity appeared to have reached a peak.

Anatomy

When study of a cell was completed, its location was marked by passing DC current (50 μA for 20 seconds) through the recording electrode. At the end of the experiment, the portion of the spinal cord studied was removed and placed in 10% formalin. After at least 3 days, the cord was frozen and cut into 60-μm sections. Sections containing the lesions were projected and drawn on paper. Laminar location of the cell was extrapolated from laminae of the cat spinal cord (Rexed, 1954). The location of the thalamic electrode was marked by passing DC current (20 μA for 20 seconds) through the thalamic-stimulating electrode. In each case, the electrode was located in VPL.

Statistics

All data are expressed as mean ± SE. Comparisons between background activity and a single response were made by means of a t-test for paired data. Multiple comparisons were made with a one-way analysis of variance. When F ratio values were found to exceed the critical value (P < 0.05), Dunnett's test was used to compare means. Analysis of variance was also used to determine linearity of regression (Zar, 1974).
Results

Seventy-one ST neurons with viscerosomatic convergent inputs were tested for responses to LTV stimulation. Forty-three (61%) were inhibited, nine (13%) were excited, three (4%) were excited and then inhibited, and 16 (22%) did not respond. A detailed analysis of these responses, as well as vagal inhibitory effects on responses to somatic stimuli, was reported elsewhere (Ammons et al., 1983). Of the neurons inhibited by LTV stimulation, 30 were tested for inhibitory responses to LTV stimulation during electrical stimulation of sympathetic afferent fibers, during intracardiac injections of bradykinin, or both. Twenty-five of these cells had some degree of background activity which was reduced from 13.2 ± 3.1 to 2.1 ± 1.7 spikes/sec (P < 0.001) by LTV stimulation. In addition, mean arterial pressure de-
creased from 88 ± 7 to 74 ± 9 mm Hg (P < 0.01), and heart rate decreased from 202 ± 8 to 173 ± 11 beats/min (P < 0.001). Cell activity usually began to decrease immediately after the beginning of LTV stimulation and recovered shortly after stimulation ended, whereas the cardiovascular changes occurred more slowly.

Histological reconstruction of laminar sites was successful for 27 of the 30 cells. Cells were located in the 2nd to 5th thoracic segments, but 21 of the 27 were in the 3rd or 4th segments. Sixteen (59%) were located in lamina IV of the dorsal horn, 8 (30%) were found in lamina V, and only 3 (11%) were in lamina VII. None were found in lamina I. It should be noted, however, that in another study we found a few lamina I cells which could be inhibited by LTV stimulation (Ammons et al., 1983).

**Sympathetic Afferent Stimulation**

The CT technique was used to examine the time course of the interaction between vagal afferents and sympathetic afferents for 19 ST cells. This information is helpful in determining whether the interaction occurs at a presynaptic site. Conditioning stimuli applied to LTV reduced sympathetic afferent test responses of 15 of these cells. Figure 1A shows a post-stimulus histogram of a cell response to the sympathetic afferent test stimulus only. The cell responded with an early peak of activity which had an onset latency indicative of Aβ fiber input. The oscilloscope tracing above the histogram shows this early cell activity as a burst of five spikes 4 msec after the stimulus artifact. Also shown in the tracing are two later spikes that occurred at a latency of 33 msec, indicative of C fiber input. C fiber activity is shown in the histogram as a second, more prolonged response peak. Figure 1B shows the cell response when the vagal conditioning stimulus was applied 30 msec before the test stimulus. The train of vagal conditioning stimuli was applied at the time indicated by the first arrow. A brief cell discharge followed LTV stimulation. The histogram of Figure 1B shows the initial vagal excitation as a peak prior to the test response. This initial brief excitation, followed by prolonged inhibition, occurred for five cells when LTV was stimulated at 1 Hz, but inhibition only was observed at higher stimulus frequencies. The reduced number of spikes occurring after the second arrow indicates that LTV stimulation did inhibit the response to the sympathetic afferent test stimulus. In this particular tracing, two late spikes were present, but over the course of 50 stimulus trials, the number of later spikes was substantially reduced. The test response was reduced to 33% of control for the Aβ peak and 30% for the C fiber peak. Figure 1C shows the response when the CT interval was increased to 50 msec, the interval of maximal inhibition. The test responses for both fiber groups began to return toward control at longer CT intervals, as shown in Figure 1D. In Figure 1E, the data for cell responses to Aβ and C fibers are plotted as the percent of the control test response.

The inhibitory effect of LTV stimulation could have resulted from excitation of afferents from a variety of sources, including abdominal and thoracic viscera. To determine whether cardiac afferents participated in these responses, we compared LTV stimulation and stimulation of the cardiac branch of the vagus for two cells. For both cells, stimulation of the cardiac branch elicited inhibition that was similar in magnitude to that resulting from LTV stimulation. Thus, for these two cells, most of the inhibition appeared to originate from cardiac vagal afferents.

Figure 2 shows the averaged CT curve for all 15 cells. The curve demonstrates the triphasic nature of vagal effects on responses to Aβ sympathetic fiber activation. Following maximal inhibition near a CT interval of 50 msec, the response began to recover near a CT interval of 80 msec. However, there followed a secondary, prolonged inhibitory trend. The CT curve was simpler for the three cells examined for C fiber input. The point of maximal inhibition occurred slightly earlier, and there was a more prolonged period of inhibition without the intervening recovery phase.

CT curves of four cells were obtained after vagotomy. In each case, little or no inhibition occurred at each CT interval. Two of these cells evoked an initial burst of cell activity followed by inhibition similar to the cell described in Figure 1. Vagotomy abolished the inhibitory response but left intact the excitation. For these four cells and one additional cell, the number of spikes evoked by each sympathetic afferent stimulus before vagotomy was compared with that obtained after vagotomy. The results are shown in Table 1. Stimulus parameters for a given cell were the same before and after vagotomy. The results show that, in four out of five cases, vagotomy increased the number of spikes evoked by sympathetic afferent stimulation. Because of the small number of cells, this effect did not reach the level of significance.

**Bradykinin**

Twenty cells whose background activity was reduced by LTV stimulation were tested for responses to injection of bradykinin (2 μg/kg) into the left
TABLE 1

Effects of Vagotomy on Responses to Sympathetic Afferent Stimulation and Bradykinin

<table>
<thead>
<tr>
<th>Sympathetic afferent stimulation (spikes/stimulus)</th>
<th>Bradykinin (spikes/s)</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Before vagotomy</td>
<td>After vagotomy</td>
<td>Before vagotomy</td>
</tr>
<tr>
<td></td>
<td>Cell 063</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Cell 081</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Cell 141</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Cell 234</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Cell 574</td>
<td>6.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>3.5 ± 1.2</td>
<td>4.1 ± 1.1</td>
<td>11 ± 8</td>
</tr>
</tbody>
</table>

atrium. Bradykinin increased the discharge rate of 14 cells. Figure 3 shows an example of this response, as well as the effect of LTV stimulation. Six seconds after administration of bradykinin, the cell discharge rate increased rapidly from 9 spikes/sec to a peak of 43 spikes/sec, 3 seconds later. Stimulation of the thoracic vagus near the peak of the response resulted in reduction of cell activity from 40 to 9 spikes/sec. Stimulation at a point later in the response reduced impulse rate from 22 to 5 spikes/sec. Bradykinin injection also caused a decrease in mean arterial pressure beginning within 4 seconds, from a control level of 96 mm Hg to 44 mm Hg, 27 seconds later. Heart rate was 212 beats/min before bradykinin injection, increased transiently, and then decreased to a rate of 180 beats/min 23 seconds post-injection. LTV stimulation during the response to bradykinin had little effect on either cardiovascular parameter,

![Figure 3. Example of a response to intracardiac injection of bradykinin before (panel A) and after (panel B) vagotomy. LTV stimulation (2 msec, 6.9 V, 20 Hz) occurred during the period shown by the bars below the second trace. The rate meter averages cell activity over a 1-second period, and its output is 1 second behind unit discharge. Rate = cell discharge rate in impulses per second; Unit = output of the window discriminator with each deflection due to one cell spike; BP = blood pressure; HR = heart rate in beats/min.](http://circres.ahajournals.org/)

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even though it caused hypotension and bradycardia in the absence of bradykinin. Figure 3B shows that, after bilateral vagotomy, LTV stimulation had no effect on the response to bradykinin. The hypotensive response was present before and after vagotomy, but was less severe after vagotomy.

The relation between cell activity elicited by bradykinin administration and the inhibitory effect of LTV stimulation is plotted in Figure 4. Regression analysis was used to show that the relationship was linear in nature. Analysis of variance indicated that this linear relationship was statistically significant ($P < 0.05$). The negative slope indicates that, with increasing cell activity elicited by bradykinin injection, the relative potency of LTV stimulation became less.

Effects of LTV stimulation on cellular and cardiovascular responses to bradykinin are summarized in Figure 5. Bradykinin caused an increase in cell discharge rate from an average of $9.1 \pm 2.1$ spikes/sec to a level of $29.2 \pm 3.7$ just before LTV stimulation (Fig. 5A). Vagal stimulation reduced activity by $18$ spikes/sec to an average of $11.7 \pm 4.0$ ($P < 0.001$). Cessation of vagal stimulation caused cell activity to return to the bradykinin-stimulated level. Bradykinin invariably caused hypotension and, usually, bradycardia (Fig. 5B). LTV stimulation sometimes, but not always, intensified these effects. For four of the 14 cells that responded to bradykinin, it was possible to compare responses before and after vagotomy. Before vagotomy, LTV stimulation reduced the cell activity elicited by bradykinin from $28.4 \pm 10.1$ to $8.5 \pm 4.1$ spikes/sec. After vagotomy, cell activity during the bradykinin response, and just before LTV stimulation, was $34.7 \pm 12.5$, and during LTV stimulation, was $37.2 \pm 15.8$ spikes/sec. Table 1 shows the effect of vagotomy on the peak response to bradykinin. For three of the four cells, vagotomy increased the response. As in the case of sympathetic afferent stimulation, the number of cells tested were too small for the effect to reach the level of significance.

Five of the 14 cells not only increased their discharge rates in response to bradykinin, but also began to burst in rhythm with the cardiac cycle. An example of one of these cells is shown in Figure 6. Figure 6A shows a 6-second period of cell activity near the peak of its response to bradykinin injection. The cell burst with two to five impulses just after

![Figure 4](image-url)  
**FIGURE 4.** Linear regression plot for vagal inhibition. There was a significantly linear relation between the two variables ($P < 0.05$).

![Figure 5](image-url)  
**FIGURE 5.** Averaged responses to intracardiac injection of bradykinin and LTV effects on those responses. Panel A: cell responses; panel B: blood pressure and heart rate responses. B = background or control levels for each parameter; BK = level during the response to bradykinin just before or just after LTV stimulation; BK + V = peak response to LTV stimulation; R = recovery value; MAP = mean arterial pressure; HR = heart rate.
FIGURE 6. Example of effect of LTV stimulations on entrainment of cell activity to the cardiac cycle by bradykinin. Panel A shows an 8-second period of activity near the peak of the response to bradykinin. The cell burst with 2 to 5 action potentials near the peak of each pressure wave. Panel B: LTV stimulation began at the point indicated by the arrow. Note that cell discharge rate slowed as stimulation continued and that bursting of the cell discontinued and firing became random. Panel C: recovery of entrained cell activity following the end of LTV stimulation. ECG = electrocardiogram.

Discussion

The important finding of this study is that stimulation of vagal afferent fibers inhibits ST neuronal activity elicited by cardiopulmonary sympathetic afferents. We chose two methods of activating sympathetic afferents. The first, electrical stimulation, was used with the CT technique to examine the time course of the vagosympathetic interaction. The CT paradigm also gives information concerning mechanisms that may be involved in the inhibition. The CT curves which were generated suggest that the inhibition is effective against activity elicited by both Aδ and C fiber sympathetic afferents, and that it is long-lasting, and complex in nature. The long-lasting nature of the inhibition is consistent with, although not proof of, the presence of a presynaptic inhibitory mechanism (Schmidt, 1971; Foreman et al., 1976). Presynaptic inhibition is the result of depolarization of axon terminals resulting in decreased release of neurotransmitter. This type of inhibition lasts for 400 msec or more (Eccles et al., 1962). Post-synaptic inhibition occurs with a time course of 50 msec or less (Eccles and Sherrington, 1931). In our study, post-synaptic inhibition could be occurring and could be masked by the presynaptic mechanism. We cannot state at what point in the nervous system the inhibition is occurring. Most likely, the inhibition occurs through synaptic links with the sympathetic afferent terminals themselves, or the terminal of an interneuron which links the sympathetic afferent with the ST cell. The CT curve for Aδ sympathetic afferents revealed two points of maximal inhibition (Fig. 2). Our results do not indicate the reason for the two inhibitory maxima; however, we can speculate that LTV stimulation evoked activity in two sets of vagal fibers of different sizes. Thus, the effect of slower-conducting vagal fibers would be exerted on ST cell responses some time after the effects of larger, faster-conducting vagal afferents. Alternatively, different pathways within brain stem circuits may have been activated (see below).

The second method chosen to activate sympathetic afferents was intracardiac injections of bradykinin. For every cell tested, LTV stimulation inhibited the activity of ST neurons elicited by bradykinin. Our regression analysis showed that a linear relation existed between the level of activity elicited by bradykinin and the percent inhibition caused by LTV stimulation. In addition to reductions in frequency of cell activity, LTV stimulation also caused a change in the discharge pattern. This effect is dramatically shown in Figure 6, where the entrainment of a cell's activity to the cardiac cycle in response to bradykinin was completely lost during vagal stimulation. Together, these findings suggest that vagal activity can completely alter the form of the messages being transmitted from ST neurons to the brain, whether the coding of the messages is in the form of frequency or in the form of a pattern such as the bursting pattern of our experiments.

Our experiments show clearly that vagal fibers responsible for inhibition of ST cells are afferent fibers coursing to the brain. In each case in which
bilateral vagotomy was performed, the inhibition was abolished. We did not attempt to localize precisely the source of the receptor endings of these afferents. However, there is reason to believe they are located in the cardiopulmonary region. In this study, we found two cells which could be inhibited by stimulation of the cardiac branch of the vagus to a degree similar to that produced by LTV stimulation. In a previous study (Ammons et al., 1983), stimulation of the vagus nerve below the heart did not inhibit ST cell activity. Thus, it appears that afferents originating from the cardiopulmonary region are likely to be the source of the inhibition. Vagotomy failed to eliminate the brief excitation of two cells by LTV stimulation. Consequently, sympathetic fibers in the vagus (Randall and Armour, 1977) must have mediated this effect.

The physiological significance of our results is related to mechanisms which account for cardiac pain. Bradykinin is a pain-producing substance that causes pseudosomatic responses (Guzman et al., 1962) and is released into the coronary sinus during myocardial ischemia (Kimura et al., 1973). Bradykinin activates cardiac Aδ and C fiber sympathetic afferents (Baker et al., 1980; Lombardi et al., 1981), and its injection into the left atrium activates primarily cardiac receptors and not receptors outside the heart (Blair et al., 1982). Thus, bradykinin administration into the left atrium can be considered a noxious cardiac stimulus. This conclusion is important, because our results are the first to demonstrate that stimulation of the vagus nerve modulates neural circuitry involved in pain sensations resulting from noxious cardiac events. One possible criticism of this interpretation is that bradykinin also activates vasal chemosensitive C fibers, although not A or C mechanoreceptor fibers (Kauffman et al., 1980). If activation of vagal receptors inhibits ST cell activity, then it may seem surprising that vagotomy yielded only a slight potentiation of the ST cell response to bradykinin. There are two possible explanations.

First, repeated injections of bradykinin into the left atrium may result in tachyphylaxis of the ST cell response (Blair et al., 1982). Thus, a greater response to bradykinin following vagotomy may have been masked by this phenomenon. Another, more likely explanation is that the vagal chemosensitive fibers activated by bradykinin make a moderate contribution to the inhibition, but the excitatory input of the sympathetic afferents is much more potent. Electrical stimulation of LTV must have either excited the chemosensitive fibers to a greater degree than bradykinin, or, more likely, other vagal afferents were activated, perhaps vagal mechanoreceptors or aortic arch baroreceptors. Regardless of which possibility is true, the potential importance of our findings is not diminished. Bradykinin injected onto the left atrium affects a large number of receptors throughout the heart. However, myocardial ischemia normally occurs in more restricted regions of the heart.

Furthermore, ischemia is associated with activation of vagal Aδ and C fiber mechanoreceptors, as well as chemosensitive endings (Thoren, 1976). It is well established that the pain of angina pectoris or myocardial infarction is due to activity in sympathetic afferents (White et al., 1933; White, 1957). The vagal afferents that are activated mediate circulatory changes, including hypotension and decreased efferent sympathetic nerve activity (Kezdi et al., 1974; Felder and Thames, 1979; Thames and Abboud, 1979). The occurrence of ischemia in a restricted area of the myocardium could provide a different balance of sympathetic and vagal afferent input to ST neurons, compared with the global effects of bradykinin observed in our experiments. Indeed, it is conceivable that preferential activation of vagal afferents, rather than sympathetic afferents, could result in little or no increase in activity of the spinohalamic tract. A series of studies by Thames and co-workers (Thames et al., 1978; Walker et al., 1978; Felder and Thames, 1979) showed that preferential activation of vagal afferents can occur. They found that occlusion of the left circumflex artery was more effective in evoking vagal reflexes than was left anterior descending artery occlusion (Thames et al., 1978). Thus, the area of the myocardium over which ischemia occurs may determine the degree to which vagal afferents are activated. These findings may explain why myocardial infarction of the inferior wall results in bradycardia and hypotension but anterior myocardial infarction results in the opposite cardiovascular changes (Randall et al., 1978). Studies showing preferential activation of vagal afferents, along with our results, may also explain the large number of reports of cardiac ischemia with little or no pain (Master et al., 1969; Margolis et al., 1973). Post-mortem examinations have revealed evidence of occluded arteries in individuals who never reported pain (Master et al., 1969). Electrocardiographic evidence of myocardial infarction also occurs in patients who report little or no pain (Margolis et al., 1973). It is possible that, in these patients, vagal afferent activity is predominant during ischemia, and that activation of ascending systems involved in pain perception is prevented by this vagal activity.

The pathways over which vagal afferents exert their inhibitory effects probably include brain stem networks and descending bulbospinal pathways. Vagal afferents terminate in or near the nucleus of the solitary tract (NTS; Beckstead and Norgren, 1979). These afferents cause reflex vasodilation and inhibition of efferent sympathetic outflow by interacting with brainstem vasomotor circuits regulating blood pressure and cardiac function (Mark et al., 1973; Thoren, 1976). These effects presumably are exerted by bulbospinal pathways which control sympathetic preganglionic neurons. Descending spinal pathways also control the activity of dorsal horn neurons, including ST neurons. Electrical stim-
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ulation of the hypothalamus (Carstens et al., 1982), midbrain periaqueductal gray (Carstens et al., 1979), nucleus reticularis gigantocellularis (Haber et al., 1978), and nucleus raphe magnus (Fields et al., 1977; Gerhart et al., 1981) powerfully inhibits dorsal horn neurons. Furthermore, these areas, particularly the midbrain and nucleus raphe magnus, are implicated in modulation of responses to pain in conscious animals (Mayer and Price, 1976) and humans (Rich-ardson and Akil, 1977). An anatomical link between the NTS and the intermediolateral column was demonstrated (Loewy and Burton, 1978), although NTS projections to the dorsal horn have not been de-scribed. The NTS does project to the hypothalamus and medial reticular formation (Ricardo and Koh, 1978; Loewy and Burton, 1978). Thus, it is reasonable that vagal inhibition of ST neurons may be mediated by activation of descending systems in-volved in pain modulation. In support of this concept is the recent description of altered catechol-amine and serotonin levels following coronary ar-tery occlusion in areas of the rat brain related to systems involved in analgesia, including nucleus raphe magnus (Sole et al., 1983). The extent to which overlap occurs between brain circuits controlling blood pressure and those which modulate process-ing of sensory information is unknown. It is of interest, however, that analgesic drugs may cause changes in blood pressure (Eckenhoff and Oech, 1960), and that rats made hypertensive are less sensitive to pain (Zamir and Segal, 1979). Thus, it appears that some interaction between the two sys-tems occurs. Clearly, interactions between vagal af-ferents and at least one ascending sensory channel, the ST tract, do exist. Whether such interactions occur tonically or are elicited only under unusual conditions, such as myocardial ischemia, remains to be determined.

In conclusion, this study shows that vagal afferent fibers inhibit responses of ST neurons to cardiopul-monary sympathetic afferent activation, including their activation when a noxious cardiac stimulus, bradykinin, is used. Our results are the first to suggest a role for the vagus nerve in the sensation of cardiac pain. Furthermore, these results may offer an explanation for the number of reports of myocar-dial ischemia with little or no pain.

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Address for reprints: W. Steve Ammons, Ph.D., Department of Physiology & Biophysics, OU Health Sciences Center, BMSB-653, P.O. Box 26901, Oklahoma City, Oklahoma 73190.

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