Intrapericardiac injections of algogenic chemicals excite primate C1-C2 spinothalamic tract neurons

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Chandler, Margaret J., Jiahua Zhang, Chao Qin, Yu Yuan, and Robert D. Foreman. Intrapericardiac injections of algogenic chemicals excite primate C1-C2 spinothalamic tract neurons. Am J Physiol Regulatory Integrative Comp Physiol 279: R560–R568, 2000.—Extracellular potentials of 38 C1-C2 spinothalamic tract (STT) neurons in anesthetized monkeys (Macaca fascicularis) were examined for responses to intrapericardiac injections of an algogenic chemical mixture (adenosine, 10⁻³ M; bradykinin, prostaglandin E₂, serotonin, histamine, each 10⁻⁵ M). Chemical stimulation of cardiac/pericardiac receptors increased activity of 21 cells, decreased activity of 5 cells, and did not change activity of 12 cells. Cells excited by chemical stimuli received input from noxious mechanical stimulation of somatic fields; most receptive fields included the neck, inferior jaw, or head areas. Nerve ablations in 11 cells excited by intrapericardiac chemicals showed that cardiac input activated by algogenic chemicals traveled primarily in vagal afferent fibers to C1-C2 segments; phrenic or cardiopulmonary sympathetic inputs were predominant in 2 of 11 cells. These results supported the concept that activation of cardiac vagal afferents might lead to the production of referred pain sensation in somatic fields innervated from high cervical segments. MYOCARDIAL ISCHEMIA ACTIVATES both vagal and sympathetic cardiac afferent fibers (10, 40). Additionally, phrenic afferents that innervate the pericardium (29) might be activated by abnormal ventricular wall movements during myocardial ischemia (17). Cardiac pain referred to the chest and arm commonly is attributed to activation of sympathetic afferent input that enters upper thoracic segments (30, 43) and excites spinothalamic tract (STT) neurons in those and nearby segments (24).

Stimulation of vagal afferent fibers usually inhibits primate STT neurons in thoracic and lower cervical segments (1, 11). In contrast, C1-C3 STT neurons are excited by electrical stimulation of thoracic vagal fibers and also by stimulation of cardiopulmonary sympathetic or phrenic afferent inputs (13, 14). These experimental findings suggest neurophysiological explanations for the clinical phenomenon of cardiac pain referred to somatic areas innervated from high cervical segments, i.e., the neck, anterior jaw, and back of the head (36). However, effects of chemically stimulating cardiac receptors in primates to enable comparisons with effects of electrically stimulating nerves that innervate thoracic structures have not been examined previously in high cervical STT cells.

The first aim of this study was to correlate the responses of C1-C2 STT neurons to chemical stimulation of cardiac/pericardial receptors with the responses of these neurons to electrical stimulation of visceral and phrenic afferents. A mixture of algogenic compounds that are likely to activate all cardiac/pericardial nerve endings (31) was injected into the pericardial sac of anesthetized monkeys. The second goal was to determine the pathway (s) used to transmit information arising from the intrapericardiac injection of algogenic chemicals to C1-C2 spinal segments. A preliminary report of portions of this work has been published in abstract form (12).

METHODS

Experiments were performed on 22 male monkeys (Macaca fascicularis) weighing 3.9–6.9 kg. Animals and neurons used for these experiments also were used for studies not included in this report. Protocols were approved by the Institutional Animal Care and Use Committee and followed guidelines of the American Physiological Society and the International Association for the Study of Pain. Monkeys were tranquilized with ketamine (10–20 mg/kg im), and catheters were placed in the right femoral vein and artery to infuse drugs and to measure blood pressure, respectively. Anesthesia was induced with α-chloralose (40–60 mg/kg iv), animals were artificially ventilated, and muscles were paralyzed with pancuronium bromide (0.08–0.1 mg/kg iv). Anesthesia and muscle paralysis were maintained with constant infusion of pentobarbital sodium (2–4 mg·kg⁻¹·h⁻¹) and pancuronium (0.15–0.2 mg·kg⁻¹·h⁻¹). Blood pressure and pupil diameter were monitored to regulate anesthesia level. End-expiratory CO₂ was maintained at 4–5%, and core body temperature was maintained at 37 ± 1°C.
If a C1-C2 STT neuron responded to electrical stimulation of at least one nerve, then the neuron was examined for responses to chemical stimulation of cardiac receptors with modified “inflammatory soup” (23). One or three milliliters (3 ml total volume) of a mixture of algogenic chemicals (adenosine, $10^{-3}$ M, and bradykinin, serotonin, prostaglandin E2, and histamine, each $10^{-5}$ M) was injected into the pericardial sac, followed by 0.5 ml saline to flush the catheter. After $\geq 100$ s, the chemical mixture was removed via the lower catheter, and two 3-ml saline flushes were injected and withdrawn. Control activity (impulses/s) was calculated by determining the mean of 30 consecutive bins with the greatest activity in the 60 s preceding the chemical injection. Stimulus activity (impulses/s) was calculated by determining the mean of 30 consecutive bins with the greatest response during the chemical stimulus. Responses were determined by subtracting the mean of control activity from the mean of stimulus activity. Latency was defined as the time from the stimulus onset to the first bin of stimulus activity $\geq 20\%$ from control activity. Latency to peak response was defined as the time from the stimulus onset to the bin with the greatest change in activity during the chemical stimulus. Values calculated for individual neurons were the average responses to one to five intrapericardiac injections for each neuron.

If nerves fibers were ablated in 11 experiments to determine which pathways were activated chemically. To interrupt vagal fibers, left or right cervical vagi were cut with scissors or the left vagus nerve was cooled near 0°C with a cooling coil filled with polyethylene glycol. To interrupt cardiopulmonary sympathetic afferent fibers, left or right cervical vagi were cut with scissors or the left vagus nerve was cooled near 0°C with a cooling coil filled with polyethylene glycol. To interrupt cardiopulmonary sympathetic afferent fibers, left or right cervical vagi were cut with scissors or the left vagus nerve was cooled near 0°C with a cooling coil filled with polyethylene glycol. To interrupt cardiopulmonary sympathetic afferent fibers, left or right cervical vagi were cut with scissors or the left vagus nerve was cooled near 0°C with a cooling coil filled with polyethylene glycol. To interrupt cardiopulmonary sympathetic afferent fibers, left or right cervical vagi were cut with scissors or the left vagus nerve was cooled near 0°C with a cooling coil filled with polyethylene glycol. To interrupt cardiopulmonary sympathetic afferent fibers, left or right cervical vagi were cut with scissors or the left vagus nerve was cooled near 0°C with a cooling coil filled with polyethylene glycol.
cardiac inflammatory soup and locations of recording sites.

Effects of intrapericardial injections of algogenic chemicals are summarized in Table 1. The chemical stimulus increased mean activity of 21 of 38 C1-C2 STT neurons by 10.1 ± 2.5 impulses/s, decreased mean activity of 5 of 38 neurons by 4.5 ± 1.2 impulses/s, and did not change mean activity of 12 neurons. Latencies to excitatory and inhibitory responses were not significantly different between neurons that were excited or inhibited by the chemical stimulus. Overall, chemical stimulation of cardiac/pericardiac receptors increased activity of C1-C2 STT neurons from 10.7 ± 1.6 to 15.7 ± 2.8 impulses/s (P < 0.01, n = 38). Saline control injections did not significantly increase mean activity (11.8 ± 2.4 to 12.6 ± 2.5 impulses/s, n = 16). Examples of neuronal responses to intrapericardiac injections are shown in Fig. 2.

Various combinations of convergent nerve inputs were observed in response to electrical stimulation of peripheral nerves (1 Hz, 33 V, 0.1 ms). Table 2 shows the number and magnitude of excitatory responses to electrical stimulation of individual ipsilateral and contralateral nerves in C1-C2 STT neurons separated according to their responses to the chemical stimulus and in the total number of neurons. The magnitude of responses to stimulation of ipsilateral vagal and phrenic fibers was significantly greater than the responses to contralateral nerve stimulation, whereas no difference was found between mean responses to ipsilateral vs. contralateral cardiopulmonary sympathetic input. However, stimulation of ipsilateral cardiopulmonary sympathetic afferents, as well as phrenic afferents, excited neurons significantly more often than contralateral stimulations, whereas no difference in the frequency of excitatory responses was found between ipsilateral and contralateral vagal stimulations. Table 3 summarizes the different patterns of excitatory nerve inputs to C1-C2 STT neurons grouped according to responses to intrapericardiac chemicals. Neurons that were excited by the chemical stimulus (n = 21) were excited by ipsilateral phrenic stimulation and also were excited by ipsilateral vagal or sympathetic afferent input; 14 of 21 neurons were excited by electrical stimulation of both vagal and sympathetic nerve fibers.

Nerve ablations were performed to determine the pathway(s) activated by intrapericardiac chemicals for 11 C1-C2 STT neurons that were excited by the chemical stimulus. Recording site lesions of these cells were located in laminae I-V; 8 cells were recorded in the left spinal cord, and 3 cells were in the right side. The ipsilateral vagus nerve was cut or cooled first in 10 cells that were excited by electrical stimulation of ipsilateral vagal afferents; the other cell did not respond to electrical stimulation of vagal nerves. Convergent response patterns to electrical stimulation of peripheral afferent inputs and effects of ipsilateral vagal ablation are shown in Fig. 3 (n = 10). Mean control activity before and after vagal cutting or cooling was not different (16.2 vs. 16.9 impulses/s, n = 10). In contrast, mean activity to the intrapericardiac chemical stimulus before ipsilateral vagal ablation was 27.0 ± 5.1 impulses/s, whereas mean stimulus activity after ipsilateral vagal ablation was 20.2 ± 5.8 impulses/s. Overall, the mean increase in activity to intrapericardiac algogenic chemicals was reduced from 10.8 ± 2.4 to 3.3 ± 3.5 impulses/s (n = 10, P < 0.01) after interruption of ipsilateral vagal fibers.

Table 1. Effects of intrapericardial injection of chemicals on C1-C2 STT neurons

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>Control Activity, impulses/s</th>
<th>Stimulus Activity, impulses/s</th>
<th>Latency, s</th>
<th>Peak Latency, s</th>
<th>Mean No. Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitation</td>
<td>21</td>
<td>11.0 ± 2.1</td>
<td>21.1 ± 4.0</td>
<td>11.1 ± 1.8</td>
<td>24.5 ± 3.3</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Inhibition</td>
<td>5</td>
<td>7.8 ± 1.9</td>
<td>3.3 ± 1.0</td>
<td>10.3 ± 1.7</td>
<td>18.2 ± 4.2</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>No response</td>
<td>12</td>
<td>11.4 ± 3.7</td>
<td>11.4 ± 4.2</td>
<td></td>
<td></td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

Values are means ± SE. Mean no. injections, average number of intrapericardiac injections/cell for each group (range 1–5 injections); STT, spinothalamic tract.
Vagal cooling was used in four experiments. Vagal damage was irreversible in one cell, but the cell still was excited when the somatic field was pinched after vagal cooling. Responses to electrical vagal stimulation returned in three cells; the response to intrapericardial chemicals recovered completely in one cell and recovered to 78 and 46% of control responses in the other two cells, respectively (Fig. 3). Different afferent inputs were tested to confirm cell responsiveness in four of five cells that showed a decrease in the effect of intrapericardial chemicals after the ipsilateral vagus nerve was cut: stimulation of the left stellate ganglion was tested in one cell after vagal and phrenic ablations (Fig. 4), input from the left phrenic nerve activated one cell, somatic stimulation activated one cell, and mechanical stimulation of the pericardium by pulling on the catheter was used to confirm responsiveness of one cell.

In 7 of 10 individual neurons shown in Fig. 3, excitatory responses to intrapericardial chemical injections were eliminated (i.e., reduced to <2 impulses/s) after interruption of ipsilateral vagal fibers. The response to the chemical stimulus was reduced, but not eliminated, in 2 of 10 neurons after vagal ablation (Fig. 3). In the example shown (Fig. 4), the response remaining after cutting the vagus nerve was eliminated after ipsilateral phrenic ablation. The cell that retained some response to the chemical stimulus after vagal cooling (Fig. 3) was tested after bilateral phrenic ablation; the excitatory effect of intrapericardial chemicals was reduced slightly from 7.1 impulses/s (after vagal cooling and warming) to 5.4 impulses/s after phrenic cooling and warming.

### Table 2. Incidence (n) of excitatory responses to electrical stimulation of nerve fibers for neurons grouped according to the response to intrapericardial chemicals and for all neurons excited by at least 1 nerve stimulus

<table>
<thead>
<tr>
<th>Chemical Response</th>
<th>Ipsilateral Nerve</th>
<th>Contralateral Nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPSA</td>
<td>VAG</td>
</tr>
<tr>
<td>Excitation</td>
<td>1.9 ± 0.8*, (n = 17)*</td>
<td>7.1 ± 1.6*, (n = 16)</td>
</tr>
<tr>
<td>Inhibition</td>
<td>2.8 ± 0.5, (n = 3)</td>
<td>4.0 ± 0.1, (n = 2)</td>
</tr>
<tr>
<td>No response</td>
<td>2.6 ± 0.6*, (n = 8)</td>
<td>9.2 ± 1.3*, (n = 8)</td>
</tr>
<tr>
<td>Total neurons</td>
<td>2.2 ± 0.5*, (n = 28)*</td>
<td>7.5 ± 1.1*, (n = 26)</td>
</tr>
</tbody>
</table>

Values are means ± SE in impulses/stimulus [average discharges evoked/stimulus ± SE for 200 poststimulus bins (1-ms bins) of histograms]. CPSA, cardiopulmonary sympathetic afferents; VAG, vagal afferents; PHR, phrenic afferents. *P < 0.01, **P < 0.02, compared with response to contralateral nerve stimulation (independent t-test); ***P < 0.05, P < 0.01, χ² analysis of the number of neurons excited by an ipsilateral or contralateral nerve stimulus compared with neurons not affected by each nerve stimulus; *P < 0.01 compared with ipsilateral vagal and phrenic values.
ablations. After determining that the cell still responded to vagal and sympathetic afferent inputs, the spinal cord was transected, but this cell was lost before chemicals could be injected to discover whether activation of cardiopulmonary sympathetic afferents produced some of the response to the chemical stimulus. One neuron increased its response to intrapericardiac chemicals after the ipsilateral vagus nerve was cut (Fig. 3). Contralateral vagal ablation did not change the effect of the chemical stimulus, but bilateral phrenic ablation reduced this effect from 32.9 to 2.3 impulses/s. This neuron still responded to pinching the somatic field (neck and head) after phrenic ablations. In contrast to the majority of neurons excited by electrical stimulation of vagal fibers, the response to the chemical stimulus in this cell appeared to be relayed by activation of afferent fibers traveling in the phrenic nerve.

The neuron that was not included in Fig. 3 because it did not receive input from electrical stimulation of vagal fibers was activated by stimulating across the left stellate ganglion and responded to a lesser extent to stimulation of left phrenic fibers. The first intrapericardial injection of algogenic chemicals increased cell activity by 36.9 impulses/s. The average increase to chemical stimulation of cardiac/pericardiac receptors was 44.2 impulses/s (3 trials); repeated injections appeared to sensitize this neuron to chemical stimulation of cardiac/pericardiac receptors. Spinal blockade with lidocaine injected midway between the C7 and C8 dorsal roots eliminated the excitatory response to the chemical stimulus. Control cell activity was stable and high (41.3 impulses/s) before intrapericardiac injection of chemicals and was 18.7 impulses/s at the time the chemicals were withdrawn from the pericardial sac. The gradual decline in spontaneous activity continued until the cell lost all spontaneous activity (3.5 min from the onset of the injection of chemicals). We concluded that input to this neuron from chemical activation of cardiac/pericardiac receptors traveled primarily via cardiac sympathetic afferents. Effects of phrenic fibers activated by the chemical stimulus cannot be ruled out, but the site of lidocaine injection was below the spinal segments of phrenic afferent input. The large somatic field of this neuron included the ipsilateral chest, back, and arm and was consistent with somatic dermatomes innervated from upper thoracic and lower cervical spinal segments.

Excitatory somatic receptive fields for the C1-C2 STT neurons examined in this study usually included ipsilateral neck/inferior jaw and head regions (Fig. 4C). The entire somatic field of one neuron was on the lower back; this cell was inhibited by intrapericardiac injection of chemicals. Two neurons had somatic fields that were located exclusively on distal forelimb or hand; activity of these cells was not affected by intrapericardiac chemicals. Somatic fields of all other neurons were on upper body regions and included head, neck, proximal limb, or chest areas. The highest proportion of neurons (25 of 38, 66%) were excited by both innocuous brushing and noxious pinching of somatic receptive fields and were classified WDR. Nine of thirty-eight (24%) neurons were excited only by noxious pinch of receptive fields and were classified HT. Four STT neurons were excited maximally by innocuous brushing of somatic fields and were classified LT. All neurons that were excited by chemical stimulation of cardiac/pericardiac receptors received noxious somatic input (14 WDR and 7 HT). Four neurons that were inhibited by intrapericardiac chemicals were WDR, one cell was LT, and no cells were HT. Of 12 cells unaffected by chemical injections, 7 were WDR, 2 were HT, and 3 were LT. Thus all LT neurons were either unaffected or inhib-

![Fig. 3. Responses of individual C1-C2 STT neurons selected for ablation of the ipsilateral vagus nerve. Intact, control response; vagus cut/cool, response after cutting or cooling the ipsilateral vagus nerve; recovery, response after rewarming the vagus nerve; dashed line, vagus cooled; solid line, vagus cut; symbols, types of afferent inputs to individual cells. CPSA, cardiopulmonary sympathetic afferents; VAG, vagus afferents; PHR, phrenic afferents; ipsi, ipsilateral; contra, contralateral.](http://ajpregu.physiology.org/10.1152/ajpregu.00605.2016)

### Table 3. Patterns of convergent excitatory nerve inputs in C1-C2 STT neurons

<table>
<thead>
<tr>
<th>Response to Chemical Stimulus</th>
<th>Excitation</th>
<th>Inhibition</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPSA</td>
<td>0 1 2</td>
<td>0 0 1</td>
<td>0 1 2</td>
</tr>
<tr>
<td>VAG</td>
<td>0 0 1</td>
<td>0 0 1</td>
<td>0 0 1</td>
</tr>
<tr>
<td>PHR</td>
<td>0 0 1</td>
<td>0 0 1</td>
<td>0 0 1</td>
</tr>
<tr>
<td>VAG, PHR</td>
<td>4 2 3</td>
<td>0 0 1</td>
<td>0 0 1</td>
</tr>
<tr>
<td>CPSA, PHR</td>
<td>3 1 2</td>
<td>0 0 1</td>
<td>0 0 1</td>
</tr>
<tr>
<td>CPSA, VAG, PHR</td>
<td>14 0 4</td>
<td>0 0 1</td>
<td>0 0 1</td>
</tr>
</tbody>
</table>
ited by intrapericardiac chemicals, and most HT neurons (7 of 9) were excited by chemical stimulation of cardiac/pericardiac receptors. \( \chi^2 \) analysis showed a difference \( (P < 0.05) \) between somatic field types of neurons that were excited by intrapericardiac chemicals compared with the combined set of neurons that was inhibited or unaffected.

**DISCUSSION**

Results of this study in primates showed that chemical stimulation of cardiac/pericardiac receptors can affect activity of C1-C2 STT neurons. All neurons examined for responses to intrapericardiac injection of algogenic chemicals were excited by electrical stimulation of at least one visceral and/or phrenic nerve. Subsequent administration of an inflammatory soup mixture into the pericardial sac changed background activity of 68% of C1-C2 STT neurons; 55% of the total number of cells examined were excited, and 13% were inhibited.

Previous studies have examined effects of chemical stimulation of cardiac receptors on neurons in the thoracic spinal cords of primates, cats, and rats (2, 7–9, 16, 21, 42). Most of these reports describe responses to application of bradykinin, which activates cardiac nerve endings and has been implicated in the production of cardiac pain (5, 27, 28, 41). In primates, 65–78% of upper thoracic STT neurons are excited by intracardiac bradykinin and few (0–6%) cells are inhibited (1, 2, 7). In cats, excitatory responses of upper thoracic
neurons after cardiac application of bradykinin range from 40 to 91% in different studies (8, 9, 21, 42). Some inhibitory responses (4–15%) are reported for unidentified spinal neurons (9, 42). In the above studies, bradykinin presumably excited neurons via sympathetic afferent fibers; vagal stimulation inhibits thoracic neurons (1, 11), and intracardiac injections would not reach phrenic receptors that innervate the pericardium (29).

A study in rats examined responses to intrapericardiac injection of bradykinin alone and to bradykinin combined with equal concentrations of adenosine, acetylcholine, histamine, serotonin, and prostaglandin E₂ (16). Behavioral testing in awake rats showed that bradykinin is necessary but not sufficient to produce aversive reactions; rats rapidly acquired passive avoidance behavior with intrapericardiac injection of the complete mixture of chemicals but not with bradykinin alone or the mixture of chemicals without bradykinin. In anesthetized rats, the mixture of chemicals activated thoracic spinal neurons more potently than bradykinin alone (16). That result agrees with findings of Handwerker and Reeh (23), who report that an inflammatory soup mixture of algogenic compounds excites nociceptors in a skin-nerve preparation more potently and with less tachyphylaxis than a single substance. We reasoned that stimulating cardiac/pericardiac receptors with a mixture of the algogenic chemicals used in these previous studies (16, 23) would activate C1-C2 STT neurons more effectively than a single compound. The pathway(s) for cardiac afferent fibers that results in pain referred to the neck and jaw region is not well defined, and the five chemicals used in this study have been shown to activate or sensitize cardiac vagal and/or sympathetic nerve endings (31).

Bradykinin stimulates ischemically sensitive cardiac afferents (41), is released from the heart after coronary artery occlusion (28), and is considered a potential mediator of cardiac pain (2, 7, 19, 28), although some studies report that intracoronary injection of bradykinin in patients does not produce typical angina (18, 31, 37). The excitatory responses of T1-T5 neurons to intracardiac bradykinin are believed to be caused by activation of cardiac sympathetic afferents; vagotomy does not change mean responses (8). Prostaglandin E₂ was selected because prostaglandins activate chemosensitive vagal C fibers (4) and can sensitize effects of bradykinin on cardiovascular reflexes and sympathetic afferents (33, 41). Histamine activates cardiac sympathetic afferents, and intracoronary injections in dogs produce pseudoaffective reactions (22, 34). Serotonin also produces pseudoaffective responses after intracoronary injections (22) and activates cardiopulmonary vagal afferents (31). Adenosine also has been proposed as a mediator of cardiac pain (39). Intracoronary injection of adenosine in humans produces pain similar to angina pectoris (15), and exogenous adenosine has been shown to activate cardiac sympathetic afferents (20). Another study, however, reports that ischemically sensitive cardiac sympathetic afferents do not respond to exogenous adenosine or endogenous production of adenosine (35). Chemical activators not examined in this study, such as reactive oxygen species (26), also might play a role in ischemic activation of cardiac afferent fibers.

Chemical stimulation of cardiac/pericardiac receptors did not necessarily correlate with pathways activated by electrical stimulation of nerve fibers. For example, all neurons that responded to intrapericardiac chemicals were excited by electrical stimulation of ipsilateral phrenic afferents, and 67% were excited by contralateral phrenic input. In contrast to these robust effects of electrical stimulation, ablation of nerve pathway(s) in 11 experiments showed that just 1 of 11 neurons received input primarily from chemical activation of phrenic receptors, although responses in 2 other neurons were attenuated somewhat by interrupting phrenic nerve fibers. Part of the phrenic input observed in this study likely arose from the pericardium (29), as previous data from this laboratory show that significantly more discharges are evoked in C1-C3 STT neurons to phrenic input stimulated rostral to the heart compared with phrenic input stimulated caudal to the heart (14). The lack of correlation between C1-C2 STT cell responses to electrical stimulation of phrenic inputs compared with the responses to the chemical stimulus should not be a factor of access to the pericardium. Both the pericardium and the outer layers of the heart were bathed in the chemical mixture in these experiments. Furthermore, release of pericardial chemicals, such as prostaglandins, can modulate the effects of stimulating epicardial nerve endings (32). Fisch (17) suggests that pain during myocardial abnormalities can be produced by mechanical stimulation of the pericardium with abnormal ventricular wall movements. The increase in cell activity observed during withdrawal of saline or chemicals in some experiments (Fig. 2) suggests that mechanical stimulation of cardiac/pericardiac receptors does activate some C1-C2 STT neurons, although the pathway was not determined. In any case, it appears that the chemicals used in this study have limited effects on phrenic afferent fibers innervating the pericardium.

Because myocardial ischemia excites cardiac afferents that travel in vagal or sympathetic nerves (10, 40), it is reasonable that referred cardiac pain results from activation of one or both of these afferent pathways. Typical angina pectoris in patients and the excitatory responses of primate T1-T5 STT neurons to intracardiac bradykinin or coronary artery occlusion have been attributed to activation of cardiac sympathetic afferents that enter the spinal cord at T1-T6 segments (6–9, 30, 43). The clinical finding that cardiac pain referred to the neck and jaw sometimes remains or first appears after surgical sympathectomy has led to the speculation that the vagus nerve may be involved (18, 31). Our previous study in primates shows that >50% of C1-C3 STT neurons are excited by electrical stimulation of either vagal or cardiopulmonary sympathetic fibers, with 6% of cells inhibited by either stimulus (13). In agreement with the current study, activity increases to vagal stimulation are greater than effects of stimulat-
ing the stellate ganglion (13). Chemical activation of cardiac/pericardiac receptors in this study showed that cardiac afferents could be responsible for effects in C1-C2 STT neurons. The results showed that ipsilateral vagotomy eliminated or attenuated excitatory responses to intrapericardiac chemicals in 9 of 11 neurons. A limitation of this protocol is that ipsilateral vagotomy usually was the first nerve ablation attempted. The exception to this procedure was a neuron that was not excited by electrical vagal stimulation; spinal blockade eliminated the response in this neuron. Because both vagal and sympathetic afferent fibers are activated by the algogenic mixture, it is possible that these visceral afferents interact to produce C1-C2 STT responses to the chemical stimulus. However, vagal pathways were involved in the activation of most C1-C2 STT neurons by intrapericardiac injection of algogenic chemicals. The excitatory effects of vagal input to C1-C2 STT neurons is in marked contrast to the inhibitory effects of vagal stimulation on STT neurons in C4-S1 segments (1, 11, 25).

Analysis of somatic field characteristics showed that intrapericardiac injections of algogenic chemicals were statistically more likely to excite C1-C2 STT neurons receiving nociceptive somatic input compared with cells excited primarily by innocuous brushing. The neuron described in Results, which appeared to be activated by input from chemical stimulation of sympathetic fibers, had a large somatic field that included areas of typical angina pectoris. The somatic fields of most neurons that were activated by chemical activation of vagal input were located on the inferior jaw, head, or neck. Spinothalamic tract neurons in C2 segment can receive somatic inputs from widespread areas (38). We cannot conclusively correlate the respective central entry sites for convergent somatic and visceral inputs. However, it is feasible that visceral inputs to C1-C2 segments converge preferentially on neurons with somatic fields innervated from segments near the entry point of the visceral input. In support of this speculation, the C1-C2 STT neurons that had excitatory somatic fields located exclusively on distal arm or lower body were either unaffected or inhibited by intrapericardiac chemicals; a previous study in primate STT neurons showed a statistical correlation between excitatory responses to cardiopulmonary somatic input and the incidence of proximal, but not distal, somatic fields on the upper body (24).

In summary, results of this study supported the idea that cardiac vagal afferents transmitted nociceptive information to C1-C2 STT neurons. Evidence from ablation of neural pathways showed that the majority of C1-C2 STT neurons excited by intrapericardiac chemicals received visceral input from chemical activation of cardiac vagal afferents. The effects of chemical activation of afferents traveling in sympathetic and phrenic nerves also must be considered. In addition to possible bias arising from the constant order of nerve ablation, responses of 2 of 11 cells were eliminated only by interruption of phrenic or sympathetic nerve pathways. It is not possible to establish that the responses of primate STT neurons to cardiac/pericardiac application of algogenic chemicals provide a neural mechanism of cardiac pain in patients. The specific chemicals involved in producing pain associated with cardiac dysfunctions remain an area of research, as are the appropriate physiological concentrations. Furthermore, the relationship between the concentrations of drugs injected into the pericardial sac and the concentrations that reached the relevant cardiac/pericardiac receptors cannot be determined with the current technique. Nevertheless, results of the current study are consistent with the suggestion that activation of cardiac vagal fibers might lead to production of referred pain sensation, particularly in neck and jaw regions.

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