Sinus and Atrioventricular Nodal Distribution of Sympathetic Fibers That Contain Neuropeptide Y

Margaret R. Warner and Matthew N. Levy

Neuropeptide Y and norepinephrine are localized in sympathetic nerve terminals throughout the heart. We sought to determine the functional distribution of the neuropeptide Y–containing sympathetic fibers to the sinus and atrioventricular (AV) nodal regions. We recorded cycle length, AV interval, and arterial pressure in 14 anesthetized dogs. We assessed the release of neuropeptide Y from sympathetic nerve terminals by measuring the attenuation of the vagal effects on cycle length and AV interval that occurred after unilateral ansa subclavia stimulation. Three-minute trains of right or left ansa stimulation, each applied at frequencies of 2, 5, and 10 Hz, produced a frequency-dependent inhibition of the vagal effects on cycle length and AV interval. After right ansa stimulation (10 Hz), however, the percent inhibition of the vagal effects on cycle length was 21±5% greater (p<0.001) than the percent inhibition of the vagal effects on AV interval. Conversely, after left ansa stimulation (10 Hz), the percent inhibition of the vagal effects on AV interval was 54±7% greater (p<0.001) than the percent inhibition of the vagal effects on cycle length. The vagal stimulus characteristics (frequency or voltage) did not significantly alter the percent inhibition, nor did the percent inhibition depend on the vagus stimulated (right or left vagus). We conclude that most of the neuropeptide Y–containing sympathetic fibers at the sinus node originate in right-sided ganglia, whereas most of those at the AV node originate in left-sided ganglia. (Circulation Research 1990;67:713–721)

The sympathetic nervous system richly innervates the myocardium and modulates various aspects of cardiac function.1–3 Most cardiac regions receive postganglionic sympathetic fibers that originate bilaterally in the stellate and caudal cervical ganglia.1,2,4–6 Some cardiac regions, however, are innervated predominantly by postganglionic sympathetic neurons that originate in either right or left sympathetic ganglia.4–8 This asymmetry of cardiac sympathetic innervation has been substantiated functionally and anatomically.4–8

In addition to containing stores of norepinephrine, postganglionic sympathetic neurons are now known to contain abundant stores of neuropeptide Y (NPY).9–11 Within the sympathetic nerve endings, most of the NPY is stored in large vesicles, whereas the norepinephrine is stored in both large and small vesicles.12,13 The amount of NPY released on sympathetic activation, therefore, may depend on the density of large vesicles within the sympathetic neurons that innervate a tissue or a specific region of a tissue.12–14 Moreover, although NPY and norepinephrine are released together on sympathetic activation,9,15–18 the ratio of NPY to norepinephrine release increases as the sympathetic stimulation frequency is augmented.17 This frequency-dependent release may be related to the separate storage sites of NPY and norepinephrine within the nerve terminal.13,17

In various tissues, NPY attenuates the release of norepinephrine and acetylcholine from sympathetic and parasympathetic nerve terminals, respectively.9,18–21 In the heart, NPY persistently inhibits the effects of vagal stimulation on cardiac cycle length and atrioventricular (AV) nodal conduction.22–24 Although the cardiac distribution of norepinephrine–containing sympathetic neurons has been examined extensively,1–8 little is known about the functional distribution of NPY–containing sympathetic fibers to various cardiac structures.

In the present study, therefore, we sought to determine the functional distribution of NPY–containing sympathetic fibers to the sinus and AV nodes by measuring vagally induced increases in cycle length and AV conduction before and after stimulating the right or left ansa subclavia. We used the

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sympathetically mediated attenuation of the vagal responses as a bioassay for the release of NPY in the sinus and AV nodal regions.22-24

Materials and Methods

Fourteen mongrel dogs (16-23 kg) were premedicated with morphine sulfate (2 mg/kg i.m.) and anesthetized with α-chloralose (100 mg/kg i.v.). A femoral vein was cannulated for the administration of supplemental doses of α-chloralose (20 mg/kg/hr). Saline was also infused intravenously to maintain fluid balance (100-200 ml/hr). To record arterial pressure, we cannulated a femoral artery and attached the cannula to a Statham transducer (model P23AC, Gould, Cleveland). A tracheal cannula was inserted, and positive pressure ventilation was begun. The cervical vagi were isolated, doubly ligated, and transected. Bipolar stimulating electrodes were inserted into the cardiac end of each vagus nerve.

The chest was opened transversely at the fourth intercostal space. The right and left stellate ganglia were isolated, doubly ligated, and transected. We looped bipolar stimulating electrodes (Harvard Apparatus, South Natick, Mass.) under the right and left ansae subclaviae. We sutured bipolar electrodes to the right atrium and right ventricle to record atrial and ventricular electrograms, respectively. A second bipolar electrode was sutured to the right atrial appendage for atrial pacing.

We continuously recorded the arterial blood pressure, the atrial and ventricular electrograms, the AA interval, and the AV interval on an oscillograph (model ES1000, Gould). We used the AA interval as a measure of the cardiac cycle length and the AV interval as a measure of AV conduction time. The AA and AV intervals were determined from the electrograms by an analog interval meter that was accurate to within 1 msec. The wires from the right and left ansa subclavia electrodes and the right and left cervical vagi electrodes were attached to individual stimulators (model S9, Grass Instruments, Quincy, Mass.).

Sympathetic Stimulation Protocol

The ansae subclaviae were stimulated supramaximally (7-10 V, 1-msec pulse width) either unilaterally or bilaterally, as required by protocol. We applied the sympathetic stimulation for a train duration of 3 minutes at frequencies of 2, 5, and 10 Hz.

Vagal Stimulation Protocols

We used two different vagal stimulation protocols ("unilateral" and "bilateral") to determine the functional distribution of NPY-containing sympathetic fibers to the sinus and AV nodes (Figure 1). In the unilateral stimulation experiments, we measured the effects of unilateral vagal stimulation on cycle length and AV interval, before and after ansa stimulation. With this protocol, we determined the effect of only right vagal stimulation on cycle length and of only left vagal stimulation on AV interval (during atrial pacing at a constant frequency).

![Figure 1. Schematic diagram of the unilateral and bilateral nerve stimulation protocols. With the unilateral protocol, only the right vagus (RV) was stimulated to increase the cardiac cycle length (CCL) and only the left vagus (LV) was stimulated to prolong the atrioventricular interval (AVI) before and after ansa subclavia stimulation (ANSA STIM). With the bilateral protocol, both the RV and LV were alternately stimulated to evoke increases in CCL or AVI before and after ansa stimulation.](http://circres.ahajournals.org/)

To determine whether the effect of ansa stimulation on the cardiac responses to unilateral vagal stimulation depended on which vagus we stimulated, we also used a bilateral vagal stimulation protocol (Figure 1). With the bilateral vagal stimulation protocol, we tested the effects of stimulating each vagus nerve on cycle length and on AV interval. We could then determine if the cardiac responses to right and left vagal stimulation were affected disparately by the ansa stimulation.

Unilateral Vagal Stimulation Protocol

Before right or left ansa stimulation, we adjusted the frequency of right vagal stimulation to increase the cardiac cycle length by about 100%, and we adjusted the frequency of left vagal stimulation to prolong the AV interval substantially without losing 1:1 AV conduction. The vagi were stimulated supramaximally (1.4-2.8 V, 1-msec pulse width) for a train duration of 15 seconds. The stimuli were applied alternately to the right and left vagi every other minute. This stimulation technique produced stable cardiac responses in the present and previous studies.23,24 We measured the vagal effects on AV interval only during atrial pacing at a constant frequency. We paced the right atrium at a cycle length 30-90 msec shorter than the prevailing spontaneous cycle length. The effects of vagal stimulation on cycle length and AV interval were measured before and after 3-minute trains of unilateral right and left ansa stimulation (2, 5, and 10 Hz). The six trains of ansa stimulation were applied in a random order in each dog (n=5).

Bilateral Vagal Stimulation Protocol

Before ansa stimulation, we adjusted the frequencies of right and left vagal stimulation to evoke similar increases in either cycle length or AV interval (Figure 1, Table 1). Table 1 summarizes the mean stimulation frequencies applied to the right and left vagi. Table 1 also summarizes the mean changes in cycle length and AV interval evoked by the 15-second trains of vagal stimulation before ansa stimulation. We determined
TABLE 1. Vagal Stimulation Frequencies and Control Cardiac Responses to Bilateral Vagal Stimulation Protocol

<table>
<thead>
<tr>
<th></th>
<th>RAS (5 Hz)</th>
<th></th>
<th>RAS (10 Hz)</th>
<th></th>
<th>LAS (5 Hz)</th>
<th></th>
<th>LAS (10 Hz)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagal stimulation</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
</tr>
<tr>
<td>frequency (Hz)</td>
<td>3.9±0.1</td>
<td>11.6±3.1</td>
<td>3.6±0.2</td>
<td>9.7±1.8</td>
<td>3.9±0.1</td>
<td>9.8±1.7</td>
<td>4.0±0.2</td>
<td>10.9±1.9</td>
</tr>
<tr>
<td>Change in CCL (msec)</td>
<td>505±31</td>
<td>500±28</td>
<td>510±17</td>
<td>510±17</td>
<td>520±14</td>
<td>520±14</td>
<td>505±29</td>
<td>500±32</td>
</tr>
<tr>
<td>Vagal stimulation</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
<td>RV</td>
<td>LV</td>
</tr>
<tr>
<td>frequency (Hz)</td>
<td>3.1±0.6</td>
<td>2.4±0.3</td>
<td>2.6±0.1</td>
<td>2.4±0.4</td>
<td>2.8±0.2</td>
<td>2.4±0.4</td>
<td>2.5±0.2</td>
<td>2.3±0.4</td>
</tr>
<tr>
<td>Change in AVI (msec)</td>
<td>55±7</td>
<td>55±7</td>
<td>55±11</td>
<td>56±10</td>
<td>60±12</td>
<td>58±11</td>
<td>56±11</td>
<td>56±11</td>
</tr>
</tbody>
</table>

Values are mean±SEM (n=4). Before each train of right ansa subclavia stimulation (RAS) or left ansa subclavia stimulation (LAS), we adjusted the right vagal (RV) and left vagal (LV) stimulation frequencies to evoke similar increases in either cardiac cycle length (CCL) or atrioventricular interval (AVI).

The effects of sequential right and left ansa stimulation, each at 5 and 10 Hz, on the vagally induced increases in cycle length and AV interval. Because we examined separately the AV interval and cycle length responses, a total of eight ansa stimulations were applied in random order in each dog (n=4).

Effects of Vagal Stimulation Frequency and Voltage

In the unilateral and bilateral stimulation protocols, we used a wide range of vagal stimulation frequencies to evoke increases in cycle length and AV interval (e.g., see Table 1). We designed the following protocol to determine whether the percentage inhibition of the cardiac vagal effects induced by ansa stimulation depended on the characteristics of the vagal stimulation. We evoked increases in cycle length by applying a stimulation train containing nine different frequency-voltage combinations to the right vagus. We applied vagal stimulation frequencies of 2, 4, and 8 Hz, each at stimulation voltages of 0.8±0.1, 1.2±0.1, and 2.0±0.2 V (mean±SEM, n=5). We labeled the vagal stimulation voltages as low, medium, and high. The high vagal stimulation voltage was supramaximal. The medium and low voltages were adjusted to evoke vagally induced cardiac responses that were approximately 66% and 33%, respectively, of the cardiac responses evoked with the high stimulation voltage. The nine frequency-voltage combinations were applied consecutively in random sequence to the vagus, each for a train duration of 16 seconds. We measured the cycle length responses evoked by this 144-second train (nine combinations multiplied by the 16-second duration of each train) of vagal stimulation, before and after bilateral ansa subclavia stimulation (10 Hz, 3 minutes).

Data Analysis

We used a paired t test to compare two mean values. To compare three or more means, we used analysis of variance. A significance level of p<0.05 was considered to be statistically significant. The area above certain curves was determined by integration. Data are presented as mean±SEM.

Results

Unilateral Stimulation Experiments

Figure 2 shows representative examples of the cardiac responses to our unilateral vagal stimulation protocol. In this set of experiments, we measured the effects of right or left ansa stimulation on the cycle length responses to right vagal stimulation and on the AV interval responses to left vagal stimulation. During the control period in this representative experiment (Figure 2A), we first stimulated the left vagus for 15 seconds during atrial pacing. The left vagal stimulation increased the AV interval to 161 msec from a control value of 104 msec. Approximately 15 seconds after the termination of left vagal stimulation, we interrupted the atrial pacing and allowed the heart to beat spontaneously. Then we stimulated the right vagus for 15 seconds. In response to right vagal stimulation (Figure 2A), the cycle length increased to 1,200 msec from a control value of 570 msec. After we completed the control vagal stimulations, we applied a 3-minute train of stimulation to the right ansa subclavia at a frequency of 10 Hz (Figure 2A). The cycle length decreased to 320 msec during stimulation.

After the termination of right ansa stimulation, we applied the same vagal stimulations (Figure 2B) that we had used previously (Figure 2A). Three minutes after right ansa stimulation, right vagal stimulation increased the cardiac cycle length to only 760 msec from a control value of 520 msec, and left vagal stimulation (during atrial pacing) increased the AV interval to 145 msec from a control value of 102 msec. Thus, 3 minutes after the cessation of right ansa stimulation, the vagal effects on cycle length and AV interval were inhibited by 62% and 25%, respectively. We continued to stimulate the vagi every other minute until the vagally induced cardiac responses returned to their control levels (data not shown).

Figures 2C and 2D show the effects of a 3-minute train of left ansa subclavia stimulation (10 Hz) on the vagally induced AV interval and cycle length responses. Three minutes after the cessation of left ansa stimulation (Figure 2D), the vagal effects on cycle length were inhibited by only 6%, whereas the vagal effects on AV interval were inhibited by 73%.

Figure 3 shows representative time courses of the recovery of vagally induced cycle length and AV interval responses obtained after the cessation of 3-minute trains of right (Figure 3A) and left (Figure 3B) ansa stimulation. The vagal effects on AV interval and cycle length were persistently attenuated
after the cessation of right or left ansa stimulation. Indeed, after right ansa stimulation (Figure 3A), the vagal effects on cardiac cycle length required 28 minutes to return to control. After left ansa stimulation, the AV interval response to vagal stimulation required almost as much time to recover fully (Figure 3B). The magnitude and duration of the attenuation of vagal effects at the sinus and AV nodes differed depending on whether the right or left ansa had been stimulated. After right ansa stimulation, the magnitude and duration of the inhibition of the vagal effects on cycle length was substantially greater than the magnitude and duration of the inhibition of the vagal effects on AV interval (Figure 3A). The converse was true after the termination of left ansa stimulation (Figure 3B).

To quantitate the inhibition of the vagal effects on the cardiac responses that occurred after ansa stimulation, we calculated the initial and summated inhibitions. We defined the initial inhibition as the attenuation of the first vagally induced response after the cessation of ansa stimulation. The initial inhibition was calculated as 100(Rc−Rc)/Rc, where Rc is the control vagally induced response and Rs is the first “experimental” response to vagal stimulation that we obtained after the cessation of ansa stimulation. We defined the summated inhibition as the area between a given recovery curve and the dashed horizontal line that represents the control value (100%) of the vagally induced response (see Figure 3). This area, which we determined by integration, represents the inhibitory effect of right or left ansa stimulation summed over the full duration of the response.

Figure 4 summarizes the initial and summated inhibitions of the vagal effects on AV interval and cycle length obtained after the cessation of ansa stimulation. Note that raising the frequency of right and left ansa stimulation from 2 to 10 Hz increased significantly (p<0.002) the initial and summated inhibitions of the vagally induced AV interval and cardiac cycle length responses. After left ansa stimulation (Figures 4A and 4B), the initial and summated inhibitions of the AV interval responses were
significantly greater \( p<0.003 \) than the corresponding inhibitions of the cardiac cycle length responses. Conversely, after right ansa stimulation (Figures 4C and 4D), the initial and summated inhibitions of the vagal effects on cycle length were significantly larger \( p<0.05 \) than the corresponding inhibitions of the vagal effects on AV interval.

The inhibition of the vagal effects induced by ansa stimulation overlapped substantially at the sinus and AV nodes (Figures 2–4). Although the inhibitory effects evoked by left ansa stimulation were predominant at the AV node, they also prevailed at the sinus node. Similarly, although the inhibitory effects elicited by right ansa stimulation were predominant at the sinus node, they were also manifest at the AV node.

**Bilatral Stimulation Experiments**

Figure 5 shows representative cycle length responses to our bilateral vagal stimulation protocol. During the control period (Figure 5A), right vagal stimulation increased the cycle length to 1,160 msec from a control value of 580 msec. One minute later, we stimulated the left vagus at a frequency that also increased the cycle length to 1,160 msec. We then stimulated the left ansa at a frequency of 10 Hz for 3 minutes (Figure 5A). Three minutes after left ansa stimulation (Figure 5B), the vagal effects on cycle length were not appreciably different from the control responses (Figure 5A). In contrast, 3 minutes after right ansa stimulation (Figure 5D), the effects of right and left vagal stimulation on cycle length were substantially attenuated. We continued to stimulate the vallae every other minute until the vagally induced cycle length responses returned to their control levels (data not shown).

We also examined AV interval responses to the bilateral vagal stimulation protocol. Figure 6 shows representative time courses of the recovery of the right and left vagal effects on cycle length (Figure 6A) and AV interval (Figure 6B) after the termination of ansa stimulation (10 Hz). The magnitude and duration of the inhibition of the vagal effects on cycle length evoked by right ansa stimulation were substantially greater than those evoked by left ansa stimulation (Figure 6A). Conversely, the inhibition of the vagal effects on the AV interval evoked by left ansa stimulation was much greater than that evoked by right ansa stimulation (Figure 6B). Note, however, that after each ansa stimulation, the time course of the inhibition of the right vagal effects was similar to that of the left vagal effects on either cycle length (Figure 6A) or AV interval (Figure 6B).

Figure 7 summarizes the initial and summated inhibition data from the bilateral stimulation experiments. As in the unilateral stimulation experiments (e.g., see Figure 4), raising the frequency of either right or left ansa stimulation increased significantly \( p<0.001 \) the initial and summated inhibitions. The initial and summated inhibitions of vagally induced
cycle length responses were significantly greater (p<0.001) after right than after left ansa stimulation (Figures 7A and 7B). At the AV node (Figures 7C and 7D), the initial and summated inhibitions were significantly greater (p<0.001) after left than after right ansa stimulation. Note that after any given ansa stimulation the inhibitions of the right vagal chronotropic and dromotropic effects were not significantly different (p>0.25) from the inhibitions of the corresponding left vagal effects.

**Effects of Vagal Stimulation Characteristics**

Figure 8 shows representative examples of the chronotropic responses to nine different vagal stimulation frequency-voltage combinations applied before and after bilateral ansa subclavia stimulation. During the control period (Figure 8A), vagal stimulation increased the cardiac cycle length by 95–1,300 msec above control; the increment depended on the frequency-voltage combination.

After we elicited the control responses, we stimulated the ansae subclaviae at a frequency of 10 Hz for 3 minutes. Three minutes after the cessation of ansa stimulation (Figure 8B), the cycle length responses to the vagal stimulation combinations were inhibited by 36–46%. The vagal effects on cycle length returned gradually to control. At 15 minutes after sympathetic stimulation, the vagal effects were inhibited by 9–27% (Figure 8D).

Figure 9 summarizes (n=5) the percent inhibitions of the vagally induced chronotropic responses at 6-minute intervals after the cessation of ansa stimulation. At any given time after ansa stimulation, the chronotropic responses evoked by the nine different vagal stimulation combinations were attenuated by a similar percent (p>0.55). Thus, changes in either the vagal stimulation voltage or frequency did significantly alter the percent inhibition of the vagal effects on cycle length after the termination of sympathetic stimulation.

**Discussion**

Our data show that the vagal effects on cardiac cycle length and AV nodal conduction were persistently attenuated after right or left ansa subclavia
stimulation in anesthetized dogs. Our results confirm those previous studies that demonstrated that the vagal effects on cycle length and AV interval are inhibited after bilateral sympathetic stimulation or after reflex activation of the sympathetic nervous system. Our data extend previous findings by showing that the magnitude and duration of the inhibition of the vagal effects depended on whether the right or left ansa subclavia had been stimulated. Indeed, after right ansa stimulation, the vagal effects on cardiac cycle length were significantly more attenuated than were the vagal effects on AV interval. Conversely, after left ansa stimulation, the AV inter-

**FIGURE 7.** Graphs showing initial and summed inhibitions of right (•) and left (□) vagal effects on cycle length (panels A and B) and atrioventricular (AV) interval (panels C and D) evoked by 3-minute trains of right and left ansa subclavia stimulation. Values are mean±SEM (n=4).
val responses were significantly more attenuated than were the cycle length responses. These data suggest that most NPY-containing sympathetic fibers that innervate the sinus node originate in right-sided ganglia, whereas those that innervate the AV node originate predominately in left-sided ganglia.

Although most cardiac structures are innervated richly by postganglionic sympathetic neurons that originate bilaterally in sympathetic ganglia, some cardiac regions receive a preponderance of sympathetic neurons that originate unilaterally.1,2,4–8 Investigators have determined the functional distribution of norepinephrine-containing sympathetic neurons by measuring the changes in cycle length, AV conduction, and cardiac contractility evoked by selectively stimulating cardiac autonomic nerves, including the right and left ansae subclaviae.2,3,5,6,8 We also measured a functional response (i.e., the inhibition of the vagal responses that occurred after ansa stimulation) to determine the distribution of NPY-containing sympathetic fibers to the sinus and AV nodes. Our data suggest that most such fibers to the sinus node originated in right-sided ganglia, whereas the majority of such fibers to the AV node originated in left-sided ganglia. The sinus node did, however, receive some NPY-containing sympathetic fibers that originated on the left side, whereas the AV node was innervated by some such fibers that originated on the right side. Thus, both nodal regions were bilaterally innervated by NPY-containing sympathetic fibers, but the distributions were asymmetrical. The asymmetry in the functional distribution of these sympathetic fibers to the sinus and AV nodes parallels that of sympathetic fibers that contain norepinephrine. These functional data also agree with immunohistochemical data that show that cardiac NPY-immunoreactive and norepinephrine-containing neurons have similar distributions and densities.10,11

We used unilateral and bilateral vagal stimulation protocols to determine the functional distribution of NPY-containing sympathetic fibers. The results of these experiments showed that right or left ansa subclavia stimulation attenuated the effects of vagal stimulation on cycle length and AV interval disparately. By examining the cycle length and AV interval responses in each unilateral vagal stimulation protocol, we found that the inhibition of vagal effects at the sinus node was substantially different from that at the AV node after right or left ansa stimulation (Figures 2–4). The bilateral vagal stimulation experiments demonstrated that the disparate effects of ansa stimulation at the sinus and AV nodes were independent of the vagus stimulated (Figures 5–7). Thus, in the bilateral stimulation experiments we found that, after ansa stimulation, the inhibition of right vagal effects was similar in magnitude and duration to the inhibition of left vagal effects. These data support our hypothesis that most NPY-containing sympathetic fibers to the sinus node originate in right-sided ganglia, whereas most of those fibers to the AV node originate in left-sided ganglia.

Our data also show that the percent inhibition of the cardiac vagal effects after ansa stimulation did not depend on the frequency or voltage of the vagal stimulus (Figures 8 and 9). Therefore, the various right and left vagal stimulation frequencies that were applied in the unilateral and bilateral vagal stimulation experiments did not account for the substantial differences in the attenuation of vagal effectiveness at the sinus and AV nodes after ansa stimulation.

NPY has been shown to be released with norepinephrine in response to sympathetic activation in humans and other mammals.15–18 NPY elicits various physiological effects, including inhibition of neurotransmitter release and direct vasoconstriction of many vascular beds.9,16,18,21 Thus, NPY may act as a neurotransmitter or neuromodulator of the autonomic nervous system. Our data indicate that the functional distribution of NPY-containing sympathetic fibers to the sinus and AV nodes is asymmetric. Thus, unilateral activation of the ansa subclavia produced a heterogeneous distribution of neurally released NPY in the cardiac tissues and evoked inhomogeneities in cardiac vagal effectiveness.

The persistent attenuation of vagal effectiveness after sympathetic activation has been attributed to the release of NPY from sympathetic nerve terminals.20,22–24 The attenuation of the vagal effects evoked by sympathetic stimulation remains after combined α- and β-adrenergic receptor blockade, and it is mimicked by exogenous NPY, but not by exogenous norepinephrine.22–24 NPY appears to inhibit cardiac vagal effects by diminishing the release of acetylcholine from vagal nerve terminals.19–21 Indeed, Potter20 showed in anesthetized dogs that the increases in cardiac cycle length evoked by bethanecol, a muscarinic agonist, were not substantially affected by exogenous NPY, whereas the increases in cycle length evoked by vagal stimulation were persistently inhibited. Although these results suggest strongly that NPY released from sympathetic nerve terminals inhibits cardiac vagal effects, we cannot exclude the possibility that other mechanisms may also play a role. NPY antagonists would enhance our ability to fully characterize the role of NPY in neural control of the heart and to determine whether NPY alone mediates the persistent inhibition of vagally induced cardiac responses that occurs after sympathetic activation.

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References


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