Parasympathetic inhibition of sympathetic effects on atrioventricular conduction in anesthetized dogs

YUJI HOYANO, YASUYUKI FURUKAWA, MIHO KASAMA, AND SHIGETOSHI CHIBA
Department of Pharmacology, Shinshu University School of Medicine, Matsumoto 390, Japan

Hoyano, Yuji, Yasuyuki Furukawa, Miho Kasama, and Shigetoshi Chiba. Parasympathetic inhibition of sympathetic effects on atrioventricular conduction in anesthetized dogs. Am. J. Physiol. 237 (Heart Circ. Physiol. 42): H1800–H1806, 1997.—To investigate the selective parasympathetic control of atrioventricular (AV) conduction during sympathetic activation, we studied the effects of cervical vagus nerve stimulation on the positive dromotropic responses to sympathetic interventions before and after surgical dissection of dual fatty tissues at the junction of the inferior vena cava and inferior left atrium and at the right atrial side of the atrial junctions of the right pulmonary veins in open-chest anesthetized dogs. In atrial-paced hearts, vagus stimulation at low frequencies prolonged atrio-His (A-H) interval and at high frequencies induced second- and third-degree AV blocks. Vagus stimulation additively prolonged A-H interval shortened by stimulation of the ansae subclaviae or isoproterenol infusion. After dissection of dual fatty tissues, vagus stimulation prolonged A-H interval by only 7%. However, during sympathetic stimulation but not during isoproterenol infusion, vagus stimulation prolonged the shortened A-H interval. Atropine abolished the responses to vagus stimulation. These results suggest that even during sympathetic activation, regional vagus inputs selectively control atrioventricular conduction, and even after denervation of the regional parasympathetic nerves, presynaptic parasympathetic inhibition of the positive cardiac responses to sympathetic activation works in the heart in situ.

CARDIAC FUNCTION is regulated by tonic activity of the sympathetic and parasympathetic nervous systems, i.e., activation of the sympathetic nerves normally facilitates cardiac function, whereas activation of the parasympathetic nerves inhibits it. Parasympathetic nerve stimulation decreases heart rate more in the presence of tonic sympathetic nerve stimulation than in its absence (15, 19, 25). On the other hand, the sympathetic-parasympathetic interactions in atrioventricular (AV) conductivity observed in previous studies were not consistent. In some studies in anesthetized dogs, the increase in AV conduction time in response to vagus stimulation was not influenced by sympathetic nerve stimulation (15, 24). In other studies, however, vagus nerve stimulation during sympathetic stimulation produced either a greater increase in AV conduction time in anesthetized dogs (20) or a smaller increase in AV conduction time in anesthetized puppies (23). Thus the sympathetic-parasympathetic interactions in the AV conductivity are different from those of the sinoatrial (SA) nodal pacemaker activity.

The parasympathetic neural elements included in cardiac intrinsic ganglionated plexus in the fatty tissue overlying the right atrial side of the atrial junction of the right pulmonary veins mediate nearly all parasympathetic control of sinus rate (1, 8, 16). Additionally, it is well recognized that parasympathetic neural elements included in cardiac intrinsic ganglionated plexus in the fatty tissue at the junction of the inferior vena cava and inferior left atrium control AV conduction (1, 8, 16). We refer to the former and latter parasympathetic neural elements as the sinus rate-related parasympathetic nerves (SRRPN) and the AV conduction-related parasympathetic nerves (AVCRPN), respectively. Therefore, we refer to surgical dissection of the right pulmonary vein fatty tissue including SRRPN as SRRPN denervation and dissection of the inferior vena cava-inferior left atrial fatty tissue including AVCRPN as AVCRPN denervation, although these fatty tissues contain multiple neuronal types in addition to the parasympathetic postganglionic nerves (10, 26).

Preparation. Eleven mongrel dogs (10–19 kg body wt) were anesthetized with pentobarbital sodium (30 mg/kg iv); supplemental doses of pentobarbital sodium were given as necessary to maintain stable anesthesia. A tracheal cannula was inserted, and intermittent positive-pressure ventilation (tidal volume 20 ml/kg; frequency 14 strokes/min) was started. The chest was opened transversely at the fifth intercostal space. Each cervical vagus nerve was crushed with a tight ligature, and each stellate ganglion was ligated tightly at its junction with the ansa subclavia. These maneuvers remove almost all tonic neural activity to the heart (14).

Two bipolar electrodes were placed on the base of the epicardial surface of the right atrial appendage to record the electrical activity and to pace the atrium electrically. Atrial rate was derived from the atrial electrogram with a tachometer (model AT-600G, Nihon Kohden, Tokyo, Japan). A bipolar electrode catheter was inserted via the right femoral artery and positioned in the noncoronary cusp of the aortic valve to record His bundle electrical activity. The His bundle electrogram was filtered with a band pass of 30–300 Hz (model AP621G, Nihon Kohden). The electrograms were recorded on the oscillograph (model R7A1200, Nihon Kohden) at paper speeds of 100 mm/s. In these electrograms, the interval between the atrial deflection and the His bundle deflection...
was determined as the atrio-His (A-H) interval. Atrial rate and femoral arterial blood pressure were also recorded on the oscillograph.

To stimulate cervical vagus nerves, two copper wire electrodes were placed in each cardiac side of the cervical vagus complexes at the crushed region and connected in parallel to an electrical stimulator (model SEN7103, Nihon Kohden). The cervical vagus nerve fibers were stimulated with a pulse amplitude of 10 V with ≤0.03-ms pulse duration and frequencies of 2, 5, 10, and 30 Hz or 1-ms duration and 30 Hz for 30 s. To stimulate bilateral efferent sympathetic nerve fibers, two bipolar hook electrodes were placed on both sides of the ansa subclavia and connected to an electrical stimulator (model SEN7103, Nihon Kohden).

We removed the fatty tissue, including the intracardiac parasympathetic neural elements, at the junction of the superior vena cava and inferior vena cava by careful trimming of the fatty tissue using a thermoknife and 10% phenol (4). We refer to this procedure as AVRPN denervation. Cervical vagus stimulation with 1 ms, 10 V, and 30 Hz caused complete AV block. Thus we thought that the AVRPN were denervated almost totally when cervical vagus stimulation with 1 ms, 10 V, and 30 Hz hardly increased A-H interval (increase of ≤0.02 ms). We also removed the fatty tissue, including the intracardiac parasympathetic neural elements to the SA nodal area overlying the right atrial side of the atrial junctions of the right pulmonary veins, because some of these neural elements affect the negative dromotropic response to cervical vagus stimulation (7, 8). We refer to this procedure as SRRPN denervation. Thus we studied the dromotropic or chronotropic effects of cervical vagus nerve stimulation before and after denervation of both AVRPN and SRRPN.

Protocols. We investigated the effects of cervical vagus nerve stimulation, before and after AVRPN and SRRPN denervation, on the decrease in A-H interval in response to sympathetic interventions in the atrial-paced heart of the open-chest anesthetized dog and the effects of cervical vagus stimulation on the increase in sinus rate in response to sympathetic interventions in the unpaced heart of the open-chest dog.

First, we studied the effects of cervical vagus stimulation on the decrease in A-H interval in response to sympathetic nerve stimulation (n = 6) or isoproterenol infusion (n = 6) before and after AVRPN and SRRPN denervation in the atrial-paced heart of open-chest anesthetized dogs. To determine the A-H interval, the heart rate was held by electrical atrial pacing. The right atrium was paced with 4 V and 1-ms pulse duration at a rate of ~150 beats/min that was 40 beats/min above intrinsic sinus rate but maintained 1:1 AV transmission without Wenckebach-type AV block. Before denervation, we determined the effects of cervical vagus stimulation on A-H interval in the absence or presence of sympathetic nerve stimulation or isoproterenol infusion in the atrial-paced heart as the vagus stimulation level was changed by increasing the stimulation frequencies from 2 to 5, 10, and 30 Hz with 10 V and ≤0.03-ms pulse duration and by prolongation of the stimulation pulse duration from ≤0.03 to 1 ms with 10 V and 30 Hz (Fig. 1). The stimulation with 1 ms and 10 V at 30 Hz caused complete AV block. To confirm whether the sympathetic interventions could cause similar cardiac effects before and after denervation, we determined the increase in sinus rate in response to sympathetic nerve stimulation in unpaced hearts. We stimulated the cardiac sympathetic nerves with 10–12 V, 1 ms, and 2 Hz for 6 min, and this stimulation increased the sinus rate ~70 beats/min. We also determined the infusion rate of isoproterenol (0.2–0.4 µg·kg⁻¹·min⁻¹) that similarly increased sinus rate 70 beats/min. While the right atrium was paced at a rate of 220 beats/min, we determined the effects of cervical vagus stimulation on A-H interval. After each sympathetic intervention, at least 15 min were needed for recovery. Twenty minutes after AVRPN and SRRPN denervation, we had confirmed the minimum response to cervical vagus stimulation with 1 ms, 10 V, and 30 Hz, and we then studied the effects of cervical vagus stimulation on the positive dromotropic response to sympathetic interventions. Nerve stimulation and isoproterenol infusion with the same conditions were repeated before and after denervation.

In six animals, we tested the effects of atropine at an intravenous dose of 0.2 mg/kg on the negative dromotropic responses to cervical vagus stimulation during sympathetic intervention after AVRPN and SRRPN were denervated. Two minutes after atropine treatment, the effects of cervical vagus stimulation on the responses to sympathetic intervention were determined again.

In the second series of experiments, we investigated the effects of cervical vagus stimulation on increases in sinus rate in response to sympathetic nerve stimulation or isoproterenol infusion before and after SRRPN and AVRPN denervation in open-chest anesthetized dog hearts. In these experiments, we also removed dual fatty tissues at the right atrial side of the atrial junctions of the right pulmonary veins and at the junction of the inferior vena cava and inferior left atrium.
First, we determined the changes in sinus rate in response to cervical vagus stimulation as the stimulation level was changed by increasing the stimulation frequencies from 2 to 30 Hz with 10 V and ≤0.03-ms pulse duration and by prolongation of the stimulation pulse duration from ≤0.03 to 1 ms with 10 V and 30 Hz. We then studied the effects of cervical vagus stimulation on the positive chronotropic response to stimulation of the ansae subclaviae or isoproterenol infusion. We determined the level of sympathetic nerve stimulation or of infusion rate of isoproterenol that is required to increase sinus rate by ~70 beats/min (to 200 beats/min or greater) before the start of the experiment. The sympathetic nerves were stimulated with 2 Hz, 1-ms pulse duration, and 10–12 V for 5 min. Isoproterenol was infused at a rate of 0.2–0.4 μg·kg\(^{-1}\)·min\(^{-1}\) for 7 min. After each sympathetic intervention, at least 15 min of recovery time were needed. When we clearly observed an increase in sinus rate after cessation of cervical vagus stimulation, we stopped further experiments. Twenty minutes after SRRPN and AVCRPN denervation, we had confirmed the minimum response to cervical vagus stimulation with 1 ms, 10 V, and 30 Hz, and we then studied the effects of cervical vagus stimulation on the positive chronotropic responses to sympathetic stimulation and isoproterenol infusion in SRRPN- and AVCRPN-denervated hearts. Nerve stimulation and isoproterenol infusion with the same conditions were repeated before and after SRRPN and AVCRPN denervation.

Statistical analysis. All data are expressed as means ± SE, and the averages are for each animal. We analyzed the absolute changes in A-H interval and rate in response to interventions except where mentioned. Analysis of variance with Bonferroni’s test was used for the statistical analysis of multiple comparisons of data. P values <0.05 were considered statistically significant.

RESULTS

Cervical vagus stimulation before and after denervation of AVCRPN and SRRPN. Before removal of the fatty tissue at the junction of the inferior vena cava and inferior left atrium including the intracardiac parasympathetic neural elements to the AV nodal region, i.e., AVCRPN, and of the fatty tissue overlying the right atrial side of the atrial junction of the right pulmonary veins including the intracardiac parasympathetic neural elements to the SA nodal region, i.e., SRRPN, cervical vagus nerve stimulation prolonged A-H interval in the anesthetized dog hearts paced electrically (147 ± 9.5 beats/min) (Fig. 2). Vagus stimulation at frequencies of 2 and 5 Hz with 0.01- to 0.03-ms pulse duration and 10-V amplitude prolonged A-H interval, and at 10 and 30 Hz it caused second- and third-degree AV blocks (Fig. 2). When the level of stimulation was increased to 1-ms duration at 30 Hz, vagus stimulation caused a complete AV block. After careful denervation of the AVCRPN and SRRPN, vagus stimulation prolonged A-H interval by only 8 ± 4.5 ms at 30 Hz with 0.01- to 0.03-ms pulse duration. Even when the level of the vagus stimulation was increased by the prolongation of the stimulation pulse duration to 1 ms at 30 Hz, vagus stimulation did not prolong A-H interval (Fig. 2).

Before AVCRPN and SRRPN denervation, cardiac sympathetic nerve stimulation and isoproterenol infusion similarly increased sinus rate and decreased A-H interval in six unpaced hearts of anesthetized dogs (Table 1). After denervation, sympathetic stimulation and isoproterenol infusion increased sinus rate similarly to stimulation before denervation. However, the decrease in A-H interval induced by sympathetic stimulation was less than that by isoproterenol infusion in denervated hearts and less than the decreases in A-H interval induced by sympathetic interventions in intracardiac parasympathetic nerve-intact hearts.

Before and after AVCRPN and SRRPN denervation, resting A-H intervals were not significantly different in six atrial-paced hearts of autonomically decentralized, open-chest anesthetized dogs (Table 1). The A-H intervals during sympathetic interventions in atrial-paced hearts were not significantly different before and after denervation (Table 2).

Parasympathetic inhibition of positive dromotropic responses to sympathetic interventions before and after denervation of AVCRPN and SRRPN. Stimulation of the right and left ansae subclaviae decreased A-H interval before and after AVCRPN and SRRPN denervation. However, the positive dromotropic response to sympathetic nerve stimulation after denervation was smaller (P < 0.05) than that before denervation (Table 1).

During sympathetic nerve stimulation or isoproterenol infusion, cervical vagus stimulation at 2 and 5 Hz with ≤0.03-ms pulse duration and 10-V amplitude prolonged A-H interval, and at 10 and 30 Hz it caused second- or third-degree AV block when AVCRPN and SRRPN were intact (Figs. 3 and 4). The increases in A-H interval in response to vagus stimulation during sympathetic interventions were not significantly different from those in response to vagus stimulation alone in intracardiac parasympathetic nerve-intact hearts of open-chest anesthetized dogs (Fig. 4).

After AVCRPN and SRRPN denervation, during sympathetic nerve stimulation, cervical vagus stimulation
and sinus rate during sympathetic interventions in a
vagus nerve stimulation decreased sinus rate itself
hearts of open-chest anesthetized dogs (Table 3). Cervi-
sis increased sinus rate similarly in five unpaced
sympathetic nerve stimulation and isoproterenol infu-
sion (Fig. 5).

Parasympathetic inhibition of positive chronotropic
response to sympathetic interventions in unpaced heart
before and after AVCRPN and SRRPN denervation.
Before and after SRRPN and AVCRPN denervation,
sympathetic nerve stimulation and isoproterenol infu-
sion increased sinus rate similarly in five unpaced
hearts of open-chest anesthetized dogs (Table 3). Cervi-
cal vagus nerve stimulation decreased sinus rate itself
and sinus rate during sympathetic interventions in a
stimulation frequency-dependent manner (data not
shown). The decreases in sinus rate induced by vagus
stimulation were similar in the presence of sympa-
thetic nerve stimulation or isoproterenol infusion.

After SRRPN and AVCRPN denervation, vagus stimu-
lization hardly decreased sinus rate itself but attenuated
the positive chronotropic response to sympathetic stimu-
lization and to isoproterenol infusion as we previously
reported (4). The inhibition by vagus stimulation of the
positive chronotropic response to sympathetic stimula-
tion was greater (P < 0.01) than that of the positive
chronotropic response to isoproterenol infusion.

DISCUSSION

In the dog heart, stimulation of the intracardiac
parasympathetic neural elements at the fatty tissue at
the junction of the inferior vena cava and inferior left
atrium selectively prolongs AV conduction time (6, 8),
and denervation of the regional parasympathetic nerves
(AVCRPN) eliminates the prolongation of AV conduc-

Table 1. Cardiac values before and during sympathetic nerve stimulation or isoproterenol infusion
in AVCRPN- and SRRPN-intact and -denervated, unpaced dog hearts

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>n</th>
<th>Before</th>
<th>During Sympathetic Intervention</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>HR, min⁻¹</td>
<td>AHI, ms</td>
<td>HVI, ms</td>
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<tr>
<td>AVCRPN and SRRPN intact</td>
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<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>6</td>
<td>107±6.5</td>
<td>80±9.2</td>
<td>36±4.8</td>
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<tr>
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<td>111±8.6</td>
<td>79±9.9</td>
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<td>105±7.0</td>
<td>80±9.3</td>
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<td>AVCRPN and SRRPN denervation</td>
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<tr>
<td>Control</td>
<td>6</td>
<td>96± 4.8</td>
<td>77±8.3</td>
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<tr>
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<td>93±5.7</td>
<td>77±8.4</td>
<td>42±5.2</td>
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<tr>
<td>Isoproterenol</td>
<td>6</td>
<td>94±5.7</td>
<td>79±8.5</td>
<td>41±5.7</td>
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</tbody>
</table>

Values are means ± SE; n, no. of experiments. HR, heart rate; AHI, atrio-His interval; HVI, His-ventricle interval; AVCRPN, atrioventricular conduction-related parasympathetic nerves; SRRPN, sinus rate-related parasympathetic nerves. Cardiac sympathetic
nerves were stimulated with 2 Hz, 1-ms pulse duration, and 10–12 V for 6 min, and isoproterenol was infused at a rate of 0.2–0.4
µg·kg⁻¹·min⁻¹ for 8 min. Nerve stimulation and isoproterenol were given with same parameters and rate, respectively, before and after
AVCRPN and SRRPN denervation.

Table 2. AHI and HVI before and during sympathetic nerve stimulation or isoproterenol infusion
in AVCRPN- and SRRPN-intact and -denervated, electrically paced dog hearts

<table>
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<tr>
<th>Experimental Group</th>
<th>n</th>
<th>APR, min⁻¹</th>
<th>AHI, ms</th>
<th>HVI, ms</th>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>6</td>
<td>147±9.5</td>
<td>101±12.9</td>
<td>36±4.7</td>
</tr>
<tr>
<td>Sympathetic</td>
<td>6</td>
<td>220</td>
<td>72±5.9</td>
<td>36±4.6</td>
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<tr>
<td>Isoproterenol</td>
<td>6</td>
<td>220</td>
<td>71±4.8</td>
<td>37±4.5</td>
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<tr>
<td>AVCRPN and SRRPN denervation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control</td>
<td>6</td>
<td>137±8.0</td>
<td>109±11.1</td>
<td>42±5.8</td>
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<tr>
<td>Sympathetic</td>
<td>6</td>
<td>220</td>
<td>89±11.4</td>
<td>42±6.0</td>
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<tr>
<td>Isoproterenol</td>
<td>6</td>
<td>220</td>
<td>79±6.5</td>
<td>41±6.5</td>
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</table>

AHI and HVI values are means ± SE; n, no. of experiments. APR, atrial rate paced electrically. Cardiac sympathetic nerves were
stimulated with 2 Hz, 1-ms pulse duration and 10–12 V for 6 min, and isoproterenol was infused at a rate of 0.2–0.4
µg·kg⁻¹·min⁻¹ for 8 min. Nerve stimulation and isoproterenol were given with same parameters and rate, respectively, before and after
AVCRPN and SRRPN denervation.

Fig. 3. Effects of cervical vagus stimulation at 5 different levels on positive dromotropic responses to sympathetic nerve stimulation (A)
and isoproterenol infusion (B) before (○) and after (●) denervation of SRRPN and AVCRPN in 6 open-chest anesthetized dog hearts
under atrial pacing. Vertical bars, SE. Dashed line, basal A-H interval (mean 101 ms). Pulse amplitude of stimulation was 10 V.
were stimulated with 30 Hz, 1 ms, and 10 V. before cervical vagus stimulation. Vertical bars, SE. Cervical nerves AVCRPN were removed. Values are percent changes from level just stimulation in 6 anesthetized dog hearts after both SRRPN and responses to cervical vagus stimulation during sympathetic nerve Fig. 5. Effects of atropine (0.2 mg/kg iv) on negative dromotropic in the AVCRPN- and SRRPN-denervated hearts. These results suggest that the negative dromotropic response to cervical vagus stimulation is mediated almost totally by AVCRPN at rest and during sympathetic activity in the heart in situ and that, in addition to the postsynaptic parasympathetic inhibition of the sympathetic effects, presynaptic parasympathetic inhibition works functionally although the parasympathetic inhibition threshold for postsynaptic inhibition is much lower than that for presynaptic inhibition.

AVCRPN denervation. To elucidate the role of the AVCRPN on AV conduction when sympathetic nerves are activated, we investigated the effects of cervical vagus stimulation on A-H interval during sympathetic interventions, i.e., sympathetic nerve stimulation and isoproterenol infusion, before and after AVCRPN and SRRPN denervation in the dog heart. To complete the denervation of AVCRPN, we removed the fatty tissue at the junction of the inferior vena cava and lower left atrium by using a thermoknife with phenol. We considered that denervation had been completed when cervical vagus nerve stimulation did not increase A-H interval ≥20 ms, although the same vagus stimulation caused complete AV block before denervation. To elucidate the effects of the denervation procedures on the responses to sympathetic interventions, we compared the changes in sinus rate and in A-H interval in response to sympathetic interventions before and after denervation in spontaneously beating hearts. The decrease in A-H interval in response to sympathetic stimulation after AVCRPN and SRRPN denervation was less than that before the denervation, although the decrease in A-H interval induced by isoproterenol and the increase in sinus rate induced by sympathetic interventions were not different before and after AVCRPN and SRRPN denervation (Table 1). These results indicate that the AVCRPN denervation procedure removes not only AVCRPN but also some of the sympathetic nerves to the AV nodal region in the dog heart. The ventrolateral cardiac nerve is distributed to the inferior atrial, AV junctional, and ventricular tissues, and its stimulation causes shortening of AV conduction time and an induction of AV junctional rhythm (9, 17, 18). Stimulation of AVCRPN decreases AV conduction time and induces an AV junctional rhythm in atropine-treated anesthetized dogs (5, 21). Thus our denervation procedure allows us to analyze results suggest that the negative dromotropic response to cervical vagus stimulation is mediated almost totally by AVCRPN at rest and during sympathetic activity in the heart in situ and that, in addition to the postsynaptic parasympathetic inhibition of the sympathetic effects, presynaptic parasympathetic inhibition works functionally although the parasympathetic inhibition threshold for postsynaptic inhibition is much lower than that for presynaptic inhibition.

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the data of the sympathetic-parasympathetic interactions on AV conduction before and after AAVCRPN and SRRPN denervation qualitatively but not quantitatively.

Sympathetic-parasympathetic interactions on AV conduction and sinus rate. In intracardiac parasympathetic nerve-intact hearts, vagus nerve stimulation decreases sinus rate more in the presence than in the absence of tonic sympathetic interventions in anesthetized dogs as shown previously (4, 15, 19, 25), whereas the increase in AV conduction time in response to vagus nerve stimulation was not significantly influenced by sympathetic nerve stimulation (Figs. 3 and 4) as previously reported (15, 24). On the other hand, after AAVCRPN and SRRPN denervation, vagus stimulation did not prolong A-H interval during isoproterenol infusion, whereas it decreased sinus rate during isoproterenol infusion. These results suggest that, although a very small number of intracardiac parasympathetic neural elements might exist after AAVCRPN and SRRPN denervation, the denervation of AAVCRPN and SRRPN abolished the dromotropic effects of vagus stimulation in the dog heart and that the AAVCRPN almost totally mediate the negative dromotropic response to cervical vagus stimulation in the presence as well as the absence of adrenergic stimulation. However, stimulation of a small number of parasympathetic neural elements probably decreased sinus rate increased by isoproterenol because of the parasympathetic inhibition of the sympathomimetic effects on sinus rate at the postsynaptic site (4), suggesting that the parasympathetic neural regulation of sinus rate and AV conduction is different and that complex interactions exist in the heart.

After AAVCRPN and SRRPN denervation, during sympathetic stimulation, cervical vagus stimulation at a high frequency (30 Hz) increased A-H interval slightly but significantly, but at low frequencies it did not (Fig. 4). These results together with the lack of prolongation of the A-H interval in response to vagus stimulation during isoproterenol infusion suggest that presynaptic parasympathetic inhibition works functionally, although the parasympathetic inhibition threshold for postsynaptic inhibition is lower than that for presynaptic inhibition in the heart. Parasympathetic ganglionic cells as well as postsynaptic parasympathetic nerve fibers exist in the fatty tissues at the junction of the inferior vena cava and lower left atrium and at the right atrial junctions of the right pulmonary veins (3, 6, 16). Because we might have removed those neural elements, including parasympathetic ganglionic cells, the prolongation of A-H interval by vagus stimulation during sympathetic stimulation observed in the present study would be induced at the site proximal to these parasympathetic ganglia. It is well known that sympathetic-parasympathetic interactions on the heart are evoked at both the presynaptic and postsynaptic sites (12, 13). Sympathetic-parasympathetic interaction at the presynaptic site involves interactions between the terminal postganglionic vagal and sympathetic fibers, which often lie in close apposition to each other in the heart (2, 11, 13). Therefore, it is likely that intraneuronal mechanisms for sympathetic-parasympathetic interactions may partially be an extracardiac neural interaction in addition to an intracardiac neural interaction in the dog heart. However, it has been reported that there are several intrinsic cardiac ganglionated plexuses other than those we have removed, including not only cholinergic neurons but also catecholamine-sensitive and/or -producing neurons and others (10, 26). Thus we cannot rule out the possibility of the participation of other innervation, from nerves that do not pass through the intrinsic cardiac ganglia we have removed, in presynaptic inhibition of the positive dromotropic response to sympathetic nerve activation.

We confirmed that in the SRRPN- and AAVCRPN-denervated heart of the anesthetized dog, cervical vagus stimulation hardly decreased sinus rate, but it depressed the sinus rate increased by isoproterenol as well as by sympathetic stimulation as previously reported (4). SRRPN stimulation during sympathetic nerve stimulation decreases sinus rate more than SRRPN stimulation alone in the anesthetized dog heart (22). On the other hand, vagus stimulation after AAVCRPN and SRRPN denervation did not affect the A-H interval during isoproterenol infusion significantly (Figs. 3 and 4). Thus the postsynaptic inhibition by vagus stimulation of sinus rate would be more complex than that of AV conduction in the dog heart in situ.

Address for reprint requests: Y. Furukawa, Dept. of Pharmacology, Shinshu Univ. School of Medicine, Matsumoto 390, Japan.

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