Modulation of guinea pig intrinsic cardiac neurons by prostaglandins

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Jelson, Gregory S., Gina M. DeMasi, Kristen L. Sager, and Jean C. Hardwick. Modulation of guinea pig intrinsic cardiac neurons by prostaglandins. Am J Physiol Regul Integr Comp Physiol 285: R682–R689, 2003. First published June 5, 2003; 10.1152/ajpregu.00123.2003.—Activation of cardiac mast cells has been shown to alter parasympathetic neuronal function via the activation of histamine receptors. The present study examined the ability of prostaglandins to alter the activity of guinea pig intracardiac neurons. Intracellular voltage recordings from whole mounts of the cardiac plexus showed that antigen-mediated mast cell degranulation produces an attenuation of the afterhyperpolarization (AHP), which was prevented by the phospholipase A2 inhibitor 5,8,11,14-eicosatetraynoic acid. Exogenous application of either PGD2 or PGE2 produced a biphasic change in the membrane potential and an inhibition of both AHP amplitude and duration. Examination of prostanoid receptors using bath perfusions (1 μM PGE2 and PGD2), specific agonists (BW245C, sulprostone, and butaprost), and antagonists (AH6809 and SC19220) found evidence for both the PGE2-specific EP2 and EP3 receptors, but not for EP1 or the PGD2-specific prostaglandin (DP) receptors. Sulprostone was able to mimic the PGE2 responses in some cells, but not in all PGE2-sensitive cells. Butaprost was able to mimic the PG-induced hyperpolarization in some cells, but did not alter the AHP. Inhibition of specific potassium channels with either TEA, charybdotoxin, or apamin showed that neither TEA nor charybdotoxin could prevent the PGE2-induced AHP attenuation. Apamin alone inhibited AHP duration, with PGs having no further effect in these cells. These results demonstrate that guinea pig intracardiac neurons can be modulated by PG, most likely through either EP2, EP3, or potentially EP4 receptors, and this response is due, at least in part, to a reduction in small-conductance Kca currents.

parasympathetic; prostaglandin E2; prostaglandin D2; prostanoid receptor; K channels

AUTONOMIC GANGLIA are integration sites for a variety of neuronal inputs, both central and peripheral (1, 13). These ganglia consist of a heterogeneous population of cells, including postganglionic neurons and numerous interneurons (1, 6, 13, 19). In addition to neuronal modulation, there is also increasing evidence for interactions between the immune system and the nervous system (11, 14, 16). Many neurons demonstrate direct modulation by autacoids, such as histamine, prostaglandins, and leukotrienes (2, 3, 8–11, 16, 20). Thus activation of the immune system in response to chemical stimulation, injury, or antigen exposure can result in direct and rapid modulation of nearby neurons. This is of particular importance in tissues with high concentrations of mast cells, the primary source of neuroactive autacoids. Examples of this type of interaction have been demonstrated in the lung (14), superior cervical ganglia (5, 20), and in the heart (16).

The mammalian heart has a particularly high concentration of mast cells in many species (21). The intrinsic cardiac plexus of the mammalian heart contains multiple cell types and inputs, including parasympathetic postganglionic neurons, interneurons, central preganglionic inputs, sympathetic fibers, and sensory fibers (1, 4, 13, 19). Previous studies in the guinea pig demonstrated that cardiac mast cells could be found in close proximity to, and even within, intracardiac ganglia located in the wall of the atria. Stimulation of the mast cells, which results in the release of histamine, caused a prolonged depolarization of the intracardiac neurons and an increase in excitability via neuronal H1 receptors (16). Similarly, in the canine heart, a population of histaminergic neurons can play a role in regulating cardiac function via H1 receptors on intrinsic neurons as well (2). Other studies in the superior cervical ganglion showed that mast cell degranulation could also lead to changes in action potential characteristics, specifically an inhibition of the afterhyperpolarizing potential (5). In addition to preformed histamine, mast cells also synthesize and release prostaglandins and other fatty acid derivatives. Previous studies have shown that prostaglandins can also modulate neuronal activity, both via direct activation of postsynaptic receptors and through presynaptic modulation of neurotransmitter release (3, 8-10, 12, 14, 18). Given the unique position of cardiac mast cells relative to the intracardiac neurons, a local inflammatory response could result in a significant increase in prostaglandin release around the intrinsic cardiac neurons. Therefore, the present study was designed to examine the ability of prostaglandins to modulate the electrical properties of the neurons in the guinea pig cardiac plexus.

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MATERIALS AND METHODS

General methods. Guinea pigs (male or female, Charles River Canada, 300–500 g, were euthanized by CO2 inhalation and exsanguination in accordance with procedures approved by the Institutional Animal Care and Use Committee. The heart was removed and placed into ice-cold Krebs Ringer solution and exsanguination in accordance with procedures described (7). The tissue was pinned to a Sylgard-lined 60-mm petri dish and continuously perfused (6–8 ml/min) with 35–37°C Krebs Ringer solution. Drugs were applied by either inclusion in the circulating bath solution or local pressure ejection (6–9 psi, Picospritzer, General Valve) through a small-diameter (5–10 μm) glass electrode positioned 50–100 μm from the individual neuron.

Electrophysiological methods. Intracellular voltage recordings from intracardiac neurons were obtained with an AxoClamp 2B amplifier (Axon Instruments) from cells impaled with 2 M KCl-filled microelectrodes (50–80 MΩ). Data were collected, digitized, and analyzed using pClamp 8.0 (Axon Instruments). Individual neurons were used for an experiment if the membrane potential was -40 mV or below and they produced action potentials with an overshoot of at least 20 mV. The neurons were identified as parasympathetic postganglionic neurons by their morphology (~30 μm in diameter) and their basic electrical properties relative to previous studies (6, 7, 16).

Single action potentials were stimulated by positive current injection (0.1–0.7 nA, 5 ms), averaged (5–6 individual recordings), and analyzed to determine the amplitude and duration of the action potential. The amplitude and duration of the action potential was measured from the peak amplitude to the resting membrane potential. The Na+ concentration in the Krebs solution was 25 mmol/L, and the K+ concentration was 80 mmol/L. The solution contained 25 mmol/L NaHCO3, 1.2 mmol/L MgCl2, 1.2 mmol/L Na2HPO4, 25 mmol/L glucose, aerated with 95% O2-5% CO2 for a pH of 7.4. The cardiac plexus, located in the epicardium of the atria, was dissected as previously described (7). The tissue was pinned to a Sylgard-lined 60-mm petri dish and continuously perfused (6–8 ml/min) with 35–37°C Krebs Ringer solution. Drugs were applied by either inclusion in the circulating bath solution or local pressure ejection (6–9 psi, Picospritzer, General Valve) through a small-diameter (5–10 μm) glass electrode positioned 50–100 μm from the individual neuron.

RESULTS

Intracellular recordings. The guinea pig cardiac plexus consists of multiple cell types, including parasympathetic postganglionic neurons and interneurons. For these studies, the results were taken primarily from cells that can be generally classified as parasympathetic postganglionic, based on their approximate size (30 μm) and their membrane properties (6, 7, 16). A total of 72 neurons from ~50 different animals was recorded in this study. The average resting membrane potential of these cells was -51.0 ± 1.1 mV. For the majority of the cells, the average AHP amplitude was 14.4 ± 0.4 mV, with a duration of 222.4 ± 8.2 ms (n = 48). Some cells did have a significantly longer AHP (>1 s), but these represented <5% of the cells tested and were excluded from the results reported here.

Mast cell degranulation and inhibition of phospholipase A2. For the current study, we monitored action potentials before and after the stimulation of mast cell degranulation to determine any changes in the AHP. Animals were sensitized to OVA to allow antigen-mediated mast cell stimulation. Previous studies have demonstrated that OVA application to nonsensitized tissue had no effect on the membrane properties of these cells (16). Tissue from sensitized guinea pigs was perfused with Krebs containing 10 μg/ml OVA for 1 min. Single action potentials were monitored before, during, and after OVA application. Approximately 2 min after the initial application of OVA, a significant decrease in AHP duration to 182.3 ± 7.2 ms (n = 4) was observed (compared with the same cell before OVA application; Fig. 1), which represents an ~24% decrease from control values.

Prior studies showed that histamine has no significant effects on the AHP in these neurons (16). Therefore, to determine if the observed inhibition of the AHP was due to the release of eicosanoids from the mast cells, some sensitized preparations (n = 8) were pre-treated with ETYA, an inhibitor of phospholipase A2, an essential enzyme in the generation of eicosanoids, before OVA application. Addition of 20 μM ETYA alone produced no significant changes in the AHP duration (221.4 ± 21.6 ms, n = 8). Subsequent application of OVA to these ETYA-treated preparations resulted in...
only a slight reduction in the duration of the AHP (200.8 ± 24.2 ms, n = 8, P < 0.05 by t-test, AHP durations in OVA+ETYA vs. OVA alone), with an overall decrease in AHP duration in the presence of ETYA and OVA of −9.5% (Fig. 1). However, the OVA-induced depolarization and increase in excitability that has been previously described (16) were still observed in the ETYA-treated cells. There were no significant changes in AHP amplitudes in any of the treatments.

Effects of prostaglandins. Because one of the primary classes of eicosanoids released by mast cells is the prostaglandins, these substances were tested to determine if they have direct effects on the membrane properties of intracardiac neurons. Both PGD$_2$ and PGE$_2$ were applied by local pressure ejection (1- to 2-s duration, 10$^{-4}$ M) to the cells. In addition, vehicle controls of 0.1% DMSO in Krebs were also tested. There were no significant effects on any of the parameters tested with application of vehicle alone (data not shown).

Of the 60 cells tested for responses to PGD$_2$ or PGE$_2$, ~85% showed measurable changes in either resting membrane potential or action potential properties. Brief application of either prostaglandin produced a biphasic change in the membrane potential (Fig. 2) of a brief hyperpolarization, followed by a more prolonged depolarization (Table 1). PGD$_2$ produced this membrane response in 26 of 31 cells tested, and PGE$_2$ showed similar results in 25 of 29 cells tested. The resting membrane potentials for these cells averaged 48 ± 1.5 mV. The amplitudes of the two phases of the response were not significantly different between the two prostaglandins. However, the duration of the depolarizing phase was significantly longer in response to PGE$_2$ application than with PGD$_2$ (Table 1).

In addition to the change in membrane potential, prostaglandin application also resulted in a significant decrease in AHP amplitude and duration in 88% of
AHP parameters returning to control values within the same cell. This change was readily reversible, with the potential in the presence of 0.3 M PGE2, although the increase was small, with only one additional action potential produced at a given stimulus (data not shown).

In some cells, changes in neuronal excitability were also monitored. Excitability was monitored by determining the number of action potentials produced in response to a series of long (500 ms) depolarizing current pulses (0.1–0.6 nA). A total of 24 cells were tested, and all of these cells were phasic in nature, firing a single action potential at the onset of the current pulse. All of the cells tested responded to prostaglandin application with a biphasic membrane response and change in AHP. Increases in excitability were observed in a total of 7 of the 24 cells (3 with PGD2 and 4 with PGE2), although the increase was small, with only one or two additional action potentials produced at a given stimulus (data not shown).

To determine whether the prostaglandins were acting directly on the neurons or by indirectly promoting the release of other neurotransmitters, we examined the ability of the prostaglandins to alter the membrane potential in the presence of 0.3 μM TTX and 100 μM CdCl2 to inhibit synaptic transmission. There was no significant change in the biphasic membrane response to PGD2 or PGE2 in the presence of TTX and Cd2+ (Table 1).

Prostaglandin receptor characterization. Prostaglandins can act via a variety of different receptors (15). Pharmacological agents were used to determine which prostanoid receptor(s) were responsible for the effects observed. Because both PGD2 and PGE2 were able to affect the neurons, both EP and DP receptors were examined.

The DP receptor agonist BW245C, the EP2-specific agonist butaprost, and the EP1/EP3 receptor agonist sulprostone were all applied by local pressure ejection to individual neurons. BW245C application (1 s, 10−4 M) produced no observable change in the membrane potential or in the AHP parameters in five separate cells (data not shown). Butaprost application (1 s, 10−4 M) produced a brief hyperpolarization in 6 of 15 cells tested (Table 1) and had no measurable effect on the membrane potential in the remaining nine cells. There was no change in AHP amplitude or duration after butaprost application in any of the 15 cells tested (Fig. 3). Sulprostone application (1 s, 10−4 M) produced a biphasic change in the membrane potential in four of seven cells tested (Table 1) and produced no response in the remaining three cells. In addition, sulprostone caused a significant decrease in AHP amplitude and duration in six of nine cells tested (Fig. 3). In some preparations, both PGE2 and sulprostone were tested on the same cells. Of the four cells tested, two cells responded to both PGE2 and sulprostone, whereas the remaining two cells responded only to PGE2.

Known prostanoid receptor antagonists were also tested for their ability to block PGE2 responses. AH6809, which inhibits DP, EP1, and EP2 receptors, caused a small decrease in the hyperpolarizing phase of the membrane response to PGE2 in four of six cells tested. In the presence of AH6809, the average PGE2-induced hyperpolarization was 2.0 ± 0.7 mV, compared with 5.3 ± 1.7 mV in the same cells in the control solution (n = 4). AH6809 had no apparent effect on the PGE2-induced depolarization. In addition, treatment with AH6809 did not prevent the PGE2-induced decrease in AHP amplitude or duration. SC19220, a specific inhibitor of EP1 receptors, had no effect on either the membrane response to PGE2 or the AHP inhibition.

In addition to applying prostaglandins by local pressure ejection, both PGD2 and PGE2 were also applied

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**Table 1. Prostaglandin-induced membrane responses: pharmacological characterization of receptors and ionic mechanisms**

<table>
<thead>
<tr>
<th>Receptor Agonist</th>
<th>Hyperpolarization Amplitude, mV</th>
<th>Hyperpolarization Duration, s</th>
<th>Depolarization Amplitude, mV</th>
<th>Depolarization Duration, s</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGD2</td>
<td>4.3 ± 0.5</td>
<td>11.2 ± 0.8</td>
<td>4.6 ± 0.6</td>
<td>54.2 ± 5.3</td>
<td>26</td>
</tr>
<tr>
<td>PGE2</td>
<td>5.5 ± 0.9</td>
<td>10.2 ± 1.3</td>
<td>4.4 ± 0.4</td>
<td>61.4 ± 5.9†</td>
<td>25</td>
</tr>
<tr>
<td>Butaprost</td>
<td>4.0 ± 1.5</td>
<td>14.0 ± 2.7</td>
<td>ND</td>
<td>ND</td>
<td>4</td>
</tr>
<tr>
<td>Sulprostone</td>
<td>4.4 ± 2.4</td>
<td>9.1 ± 3.0</td>
<td>10.6 ± 5.6</td>
<td>53.3 ± 20.2</td>
<td>4</td>
</tr>
<tr>
<td>PGD2 + TTX/Cd2+</td>
<td>4.8 ± 1.0</td>
<td>10.2 ± 1.3</td>
<td>4.5 ± 0.7</td>
<td>61.0 ± 23.3 NS</td>
<td>6</td>
</tr>
<tr>
<td>PGD2 + TEA</td>
<td>2.5 ± 0.6†</td>
<td>14.7 ± 2.6</td>
<td>4.3 ± 1.5</td>
<td>94.0 ± 6.2†</td>
<td>4</td>
</tr>
<tr>
<td>PGE2 + Cb/Tx</td>
<td>6.9 ± 1.6</td>
<td>9.6 ± 0.9</td>
<td>4.7 ± 1.2</td>
<td>101.4 ± 14†</td>
<td>4</td>
</tr>
<tr>
<td>PGE2 + apamin</td>
<td>4.0 ± 1.1</td>
<td>15.1 ± 5.5</td>
<td>3.1 ± 0.7</td>
<td>86.6 ± 9.9†</td>
<td>6</td>
</tr>
</tbody>
</table>

Values represent means ± SE of n different cells. Membrane voltage response to a 1- to 2-s application of PGD2, PGE2, butaprost, or sulprostone (all at a concentration of 10−4 M) was determined. For some cells, the PG response was then recorded in Krebs containing either 0.3 μM TTX + 100 μM CdCl2, 10 mM TEA, 100 nM charybdotoxin (Cb/Tx), or 1 nM apamin. Statistical significance was determined by t-test as indicated. Resting membrane potentials for these cells ranged between −40 and −60 mV. ND, not detectable. *P < 0.05 vs. PGD2 duration by t-test; †P < 0.05 vs. control Ringer by paired t-test; NS, no statistical difference vs. control Ringer by paired t-test.
at a known concentration in the bath. Both prostaglandins were applied at a concentration of 1 μM for 30 s. Perfusion with 1 μM PGD₂ produced no observable changes in membrane potential (Fig. 4) or AHP characteristics (data not shown) in five cells tested. However, perfusion with 1 μM PGE₂ resulted in a biphasic membrane response (Fig. 4) and attenuation of the AHP (data not shown) in four different cells.

**Ionic mechanisms of prostaglandin responses.** A preliminary examination of the potential ionic mechanisms underlying the prostanoid-induced responses was performed using specific potassium channel inhibitors. For each inhibitor, the ability of prostaglandins to produce the biphasic membrane response and inhibition of the AHP was compared before and after incubation with the channel blockers.

All three of the potassium channel inhibitors used, TEA, CbTx, and apamin, appeared to cause an increase in the duration of the depolarizing phase of the prostaglandin-induced response. However, there were no significant changes in the amplitudes of the depolarizing phases with any of the inhibitors. TEA, an inhibitor of multiple K⁺ channels, at a concentration of 10 mM, caused a partial inhibition of the amplitude of the hyperpolarizing phase of the prostaglandin-induced membrane response (Table 1). CbTx (100 nM) and apamin (1 nM), specific inhibitors of large-conductance (BK) and small-conductance (SK) calcium-activated potassium channels, respectively, had no effect on hyperpolarizing phase of the prostaglandin-induced responses (Table 1).

TEA alone produced a decrease in the amplitude of the AHP. However, PGD₂ application to cells treated with TEA produced a further reduction in both the amplitude and duration of the AHP (Fig. 5). CbTx treatment alone did not significantly alter the AHP parameters, nor did it alter the ability of PGE₂ to further reduce the AHP duration (Fig. 5). Apamin treatment alone significantly reduced the AHP duration without affecting the AHP amplitude (Fig. 5). Application of PGE₂ to apamin-treated cells resulted in no further reduction in AHP duration compared with apamin alone.

Determination of excitability changes in the presence of the potassium channel inhibitors found that both TEA and apamin alone caused an increase in excitability, with apamin producing the most profound changes: going from a single action potential during a 500-ms pulse in the control solution to more than 20 action potentials in one cell. CbTx did not alter excitability significantly. Prostaglandin application in the presence of these inhibitors did not alter excitability to any measurable degree beyond the effects of the inhibitor alone.

**DISCUSSION**

Mast cells are found in close proximity to, often even embedded within, clusters of neurons in the guinea pig cardiac plexus (16). Previous studies demonstrated that stimulation of mast cell degranulation, leading to the release of histamine, had direct actions on the membrane properties of parasympathetic postgangli-
Antigen-mediated mast cell degranulation in sensitized animals led to a transient decrease in AHP duration of parasympathetic intracardiac neurons. Addition of the phospholipase A2 inhibitor ETYA, which would prevent the synthesis of eicosanoids by preventing the generation of arachidonic acid, resulted in a significant inhibition of the AHP modulation in response to mast cell stimulation. Histamine actions would not be inhibited in the presence of ETYA, and in fact, membrane depolarization and an increase in excitability were still observed. However, previous studies had already shown that histamine does not alter the AHP in these neurons (16). Thus the AHP attenuation observed after mast cell degranulation appears to be due to eicosanoid release from the mast cells.

Direct application of prostaglandins by either local pressure ejection or bath perfusion demonstrated that these agents could directly alter the membrane properties in the vast majority of these neurons. Brief local application of either PGE2 or PGD2 resulted in a biphasic membrane response similar to the membrane response previously observed in guinea pig gallbladder parasympathetic neurons (10). However, we saw no evidence for a third phase to the response, of a delayed slow hyperpolarization, as was reported in the gallbladder neurons. To ensure that the actions of the prostaglandins were postsynaptic and not via presynaptic actions, prostaglandins were applied in the presence of TTX and Ca2+ to prevent synaptic transmission. The membrane responses to PGD2 and PGE2 were unchanged under these conditions and thus were not dependent on synaptic release of other neurotransmitters.

In addition to the change in membrane potential, both prostaglandins also produced significant attenuation of the AHP amplitude and duration, similar to that observed after mast cell degranulation. This observation is consistent with the results seen in other autonomic neurons, where prostanoid application also resulted in an inhibition of AHP amplitude and duration (10, 12).

Characterization of the potential prostanoid receptors mediating these responses was inconclusive, primarily due to the lack of available specific agonists and antagonists for some of the receptor subtypes. Neither the DP-specific agonist BW245C nor the EP1-specific antagonist SC19220 was able to mimic or prevent (respectively) prostanoid responses, thus indicating that neither of these receptors is likely to be found on the neurons. Butaprost, the EP2-specific agonist, was able to elicit a hyperpolarization in some cells, suggesting that a subpopulation of cells may express EP2 receptors. In addition, AH6809, which blocks EP2 receptors (in addition to DP and EP1 receptors), produced a decrease in the amplitude of the prostaglandin-induced hyperpolarization in 75% of the cells tested. This would suggest that the EP2 receptor might mediate the hyperpolarizing response in some neurons. However, EP2 agonists and antagonists did not have any effect on the AHP amplitude or duration. Thus the EP2 receptor does not appear to be involved.
in the modulation of the action potential. Sulprostone, the EP1/EP3 agonist, was able to produce a biphasic membrane response similar to PGE$_2$ and PGD$_2$ in ~50% of the cells. Sulprostone was also able to attenuate the AHP in ~60% of cells. This would suggest that EP3 receptors might be responsible for at least some of the observed effects and may be able to mediate both the change in membrane potential and the modulation of the AHP in these cells. However, sulprostone was not able to mimic the effects of PGE$_2$ in all cases, even in cells that did respond to PGE$_2$. This suggests there may be additional receptors, such as EP4 receptors, present on some neurons. Further studies with selective agonists and antagonists for the EP3 and EP4 receptors are necessary to form any conclusions about the prostaglandin receptors responsible for these actions.

Although the EP receptors are selective for PGE$_3$s, at high concentrations PGD$_2$ would also be able to stimulate these receptors, with EC$_{50}$s for PGD$_2$ at these receptors often 1,000-fold or more greater than PGE$_2$ (15). The concentration of PGD$_2$ used in the local pressure application (100 μM) was probably sufficient to allow stimulation of EP receptors. However, when PGD$_2$ was applied by bath perfusion at a lower concentration (1 μM), no measurable responses were observed. Bath application of the same concentration of PGE$_2$ evoked the expected membrane responses and attenuated the AHP. Thus the pharmacological experiments support the hypothesis that these neurons may express one or more subtypes of the EP receptor family, including EP2, EP3, and possibly EP4. Given the heterogeneous nature of the neurons within the cardiac plexus, the variability in specific receptor expression may ultimately relate to the unique function of the individual neurons.

A preliminary examination of the ionic mechanisms underlying the prostaglandin-induced responses suggests that the hyperpolarizing phase of the membrane response is due to the activation of a TEA-sensitive potassium current based on the reduction in amplitude of this response in the presence of TEA. None of the inhibitors tested altered the amplitude of the depolarizing phase, although the duration was increased. This increase in duration may be nonspecific and due more to the overall increase in membrane resistance with the addition of ion channel inhibitors, rather than specific channel inhibition.

The AHP in these neurons is primarily due to the activation of K$_{Ca}$ channels. Therefore, specific inhibitors of different K$^+$ channels were used to try to determine which channels are modulated by prostaglandins. TEA, an inhibitor of several different K$^+$ channels, caused a decrease in the amplitude of the AHP, without altering the AHP duration. Application of prostaglandins to TEA-treated cells still resulted in a significant attenuation of the AHP. CTX, a specific inhibitor of BK channels, also did not alter the prostaglandin-induced inhibition. Apamin, a specific inhibitor of SK channels, significantly reduced the duration of the AHP without inhibiting the amplitude. Application of prostaglandins to apamin-treated cells did not produce any further alterations in the AHP. This would indicate that the prostaglandin-mediated attenuation occurs via the inhibition of SK channels. What was not determined from this study is whether the prostaglandins produce this affect via the inhibition of Ca$^{2+}$ channels, which would then result in fewer K$_{Ca}$ channels activated, or whether it is the result of a direct modification of SK channels. It should be noted that studies in other neuronal preparations have shown evidence for prostaglandin-induced inhibition of Ca$^{2+}$ channels (8, 9, 12). Further studies are needed to identify the specific ionic mechanisms responsible for the prostaglandin-induced changes in these neurons.

The results of this study provide further evidence for the interaction between the immune system, in the form of cardiac mast cells, and the autonomic nervous system. In addition to direct actions by histamine, this study demonstrates that prostaglandins can also alter the function of the intrinsic cardiac neurons, leading to small changes in their resting membrane potentials and an attenuation of the duration of the action potentials. This modulation of the membrane properties could result in an increased firing ability of these neurons to other stimuli. Thus local inflammatory events leading to the activation of cardiac mast cells could lead to a local modulation of intrinsic cardiac neurons, which would increase their overall output and modify cardiac function.

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DISCLOSURES

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REFERENCES