Neuronal Prostacyclin Is an Autocrine Regulator of Arterial Baroreceptor Activity

Vladislav Snitsarev, Carol A. Whiteis, Mark W. Chapleau, Francois M. Abboud

Abstract—We tested the hypothesis that neuronal prostacyclin is an autocrine regulator of arterial baroreceptor neuronal activity. In isolated rat aortic nodose baroreceptor neurons, mechanical stimulation depolarized 12 neurons by 13.1±3.4 mV and triggered action potentials in 5 of them, averaging 18.2±9.5 spikes. Current injections depolarized 21 neurons by 29.9±8.0 mV and triggered action potentials averaging 17.0±2.4 spikes. After a period of prolonged neuronal activation with pulses of 1 nA at 20 Hz for 1 minute, the action potential responses to mechanical stimulation and to current injections were first markedly suppressed (0.2±0.2 and 2.1±0.7 spikes, respectively) and then enhanced, reaching levels above control (29.0±8.0 and 21.7±2.6 spikes, respectively) over the subsequent 15 minutes. In contrast, there was no inhibition of the depolarizations caused by mechanical stimulation or current injections. The recovery and enhancement of action potentials, which reached 150±5.4% of control values at 15 minutes (n=13), were abrogated by 10 μmol/L of indomethacin and replaced by sustained inhibition for over 15 minutes. Carbacyclin (10 μmol/L) reversed the inhibition and restored action potential responses. Prostacyclin production by cultured nodose neurons was enhanced by arachidonic acid and electrical field stimulation and inhibited by indomethacin. We conclude that prostacyclin provides an autocrine feedback that restores and enhances the responsiveness of arterial baroreceptor neurons after their inhibition from excessive neuronal activation. We speculate that reduced synthesis of neuronal prostacyclin contributes to the resetting phenomenon and the suppressed activity of arterial baroreceptors in hypertension. (Hypertension. 2005; 46:1-7.)

Key Words: neurons ■ membranes ■ ion channels ■ baroreflex ■ prostacyclin

Baroreceptor neurons (BRNs) innervate the aortic arch and both carotid sinus regions and sense changes in arterial blood pressure. Sustained periods of increased arterial pressure and baroreceptor activity (BRA) often lead to upward “resetting” of the pressure–activity relation to higher pressures, with possible decreases in BRA in vivo,1–4 which provide a detrimental positive feedback for hypertension. The current view is that postexcitatory inhibition of BRA may be mediated through a hyperpolarizing effect of activated Na+−K+-ATPase.5,6 In addition, inhibition of voltage-gated Na+ channels by NO,7 which may be generated during baroreceptor stimulation through the activation of Ca2+-dependent NO synthase,8,9 may also contribute to postexcitatory inhibition. Several studies indicate that prostaglandins, and prostacyclin (PGI2) in particular, excite BRNs, as well as cardiac vagal afferents.10–13 Decreased synthesis of PGI2 may play a role in acute and chronic baroreceptor resetting and the decreased baroreceptor sensitivity in hypertension.13,14 PGI2 released by ischemic myocardium activates cardiac vagal afferents and suppresses the baroreflex.15 Although a major source of PGI2 is believed to be vascular endothelium,16,17 Wang et al14 found that removal of endothelium did not prevent the inhibitory effect of indomethacin on baroreceptors. These findings, together with the finding of Weinreich et al that PGI2 contributes to the excitatory action of bradykinin in nodose neurons of guinea pigs,18 provided a rationale for this study. Thus, we tested the hypothesis that autocrine (ie, neuronal) PGI2 plays an important role in opposing the “postexcitatory inhibition” in BRNs. We speculate that failure of endogenous neuronal PGI2 to oppose the resetting of baroreceptors and to restore their decreased activity sustains the hypertensive state.

Materials and Methods

Cultured Nodose Neurons

Rat aortic arch baroreceptors were labeled with 1,1′dioleyl-3,3,3′,3′-tetramethylindocarbocyanine methanesulfonate (DiI) retrograde tracer injected into the adventitia of the aortic arch as described previously.7,19 DiI fluorescence of labeled BRNs was detected using Rhodamine filter set on the stage of Diaphot TMD Nikon microscope (Nikon). The neurons were isolated and cultured as described previously7,19–22 (please see http://hyper.ahajournals.org).
Microelectrodes and Membrane Potential Measurements

Membrane potentials (MPs) and action potentials (APs) were recorded with sharp microelectrodes using Axoprobe-1A and Clampfit 9 software and was analyzed using Clampfit 9 (Axon Instruments; please see http://hyper.ahajournals.org).

Neuronal Activation and Measurements of Neuronal Excitability

Tonic BRNs, which generated multiple AP(s) during 1-s depolarizing currents of 0.5 nA, were selected. Repeated responses to 2 stimuli (mechanical stimulations and 1-s depolarizations) were tested before, immediately after, and 15 minutes after neuronal activation (NA), which consisted of a current of 1 nA delivered at 20 Hz for 1 minute. Mechanical stimulation was induced with puffs of buffer solutions lasting 3 s, and the depolarizing injections were 0.5-nA currents for 1 s (please see http://hyper.ahajournals.org). The recorded responses included the changes in membrane conductance (MG), MP, and in the number of generated APs. MG was calculated from the response to hyperpolarizing current injection (\(I_{\text{h}}\)) of 0.1 nA. Because fluctuations in resting MP may influence the generated APs, results were also obtained at constant resting potentials of −60 mV maintained with a hyperpolarizing current. Thus, a comparison of changes in MP, MG, and AP responses under different protocols could be made from the same resting MP of −60 mV.

Mechanical Stimulation

Neurons were mechanically stimulated with extracellular buffer ejected at 10 psi for 3 s using a pneumatic PicoPump Model PV830 (WP) from a micropipette with a tip diameter of 2 μm formed with a P-2000 puller (Sutter). The tip of the pipette was placed 10 μm from the cell surface. Depolarizing potential (ΔMP) was measured as the difference between the MP reached during the last 100 ms of a 3-s puff and the MP during 100 ms before the puff. Responses were obtained at the resting MPs, which favored the generation of APs in neurons with a lower MP. The same neurons were also tested at a fixed level of −60 mV, which gave consistent ΔMPs with mechanical stimuli but did not firing APs (please see http://hyper.ahajournals.org).

Experimental Protocols

Four protocols were followed. (1) Responses to mechanical stimulation at resting MP as well as at −60 mV (n = 12) were measured in the same neurons before, immediately after, and 15 minutes after the period of NA. (2) Responses to 1-s depolarizing current of 0.5 nA were measured at −60 mV (n = 21) before, immediately after, and several times over the period of 15 minutes after NA (<6 s, 15 s, 30 s, 1 minute, 2 minutes, 4 minutes, 10 minutes, and 15 minutes). The data reported in this protocol included 3 sets of values: before and immediately after NA (<6 s) and the peak response seen after NA within the 15-minute recovery period. (3) The effect of endogenous PGI2 on the suppression and recovery phases after NA was tested with \(I_{\text{inj}}\) delivered as in protocol 2. The data reported in this protocol included responses before NA and during each of the 8 \(I_{\text{inj}}\) after NA to portray the temporal restoration of APs in the absence of indomethacin in 13 of the 21 neurons and in the presence of indomethacin (10 μmol/L) in another group of 10 neurons. (4) In 5 neurons, we tested whether the addition of the stable PGI2 analogue carbacyclin (cPGI) in the presence of indomethacin would reverse the effect of indomethacin and restore the recovery after NA.

Statistical Analysis

Paired t test or Wilcoxon’s sign rank test were used to compare neuronal excitability before and after NA. Group data are expressed as mean ± SEM. Differences were considered significant at \(P < 0.05\).

Generation of PGI2 by Nodose Neurons in Culture

Neurons from 16 nodose ganglia of 8 rats were dissociated as described. Eight ganglia from each set of 4 rats were pooled, and the neurons were evenly distributed to 8 wells for separate analysis of 6-keto-prostaglandin F1α by ELISA assay (please see http://hyper.ahajournals.org).

Reagents

For reagents, please see http://hyper.ahajournals.org.

Results

Effect of NA on Responses to Mechanical Stimulation

NA Inhibited AP Generation But Not the Depolarizations During Mechanical Stimulation

At Resting MPs (Figure 1A and 1B)

In 12 BRNs, mechanical stimulation decreased MP by 13.1 ± 3.4 mV, but only 5 neurons fired APs. The resting MP in those 5 neurons averaged −36.2 ± 8.1 mV, with an input conductance of 8.9 ± 0.8 nS. The mechanically induced APs averaged 18.2 ± 9.5 AP spikes, which were abolished after NA and then recovered with significant enhancement by 15 minutes. The resting MP of the other 7 neurons that did not generate APs was greater (−47.4 ± 3.7 mV), and their input conductance was 10.9 ± 1.5 nS. The decreases in MP during mechanical stimulation were not altered by NA (\(P > 0.05\)).

At a Fixed Resting MP of −60 mV (Figure 1C and 1D)

When resting MP was fixed at −60 mV to eliminate differences in resting MP among the 12 neurons, they all depolarized with mechanical stimulation (Figure 1C) but did not generate APs. The ΔMPs were unaltered by NA (Figure 1D). Increases in input conductance with mechanical stimulation averaged 3.0 ± 2.3; 1.9 ± 1.4, and 1.5 ± 0.9 nS before, immediately after NA, and 15 minutes later and were not statistically different from each other (\(P > 0.05\); Figure 1C).

Effect of NA on Responses to Depolarizing \(I_{\text{inj}}\)

NA Inhibited AP Generation in Response to \(I_{\text{inj}}\) at −60 mV

Resting MP was maintained at −60 mV in 21 neurons. \(I_{\text{inj}}\) depolarized the neurons by 28.6 ± 4.7, 25.9 ± 3.1, and 29.1 ± 5.3 mV and triggered the corresponding APs of 17.0 ± 2.4, 21.7 ± 0.7, and 21.7 ± 0.7 spikes before, immediately after NA, and at the peak response seen during the subsequent 15-minute recovery period, respectively (Figure 2A). These changes in MP were not statistically different but the decrease and subsequent maximal enhancement of APs were significantly different from control before NA (\(P < 0.05\); n = 21).

Effect of Indomethacin on the Recovery of APs With \(I_{\text{inj}}\) After NA

Indomethacin Abrogated the Recovery of APs

In 13 neurons, the responses to depolarizing \(I_{\text{inj}}\) before and 8 times within 15 minutes after NA are reported here to define the temporal pattern of recovery in the absence and presence of indomethacin (Figures 2 and 3).

In the absence of indomethacin and before adjusting to −60 mV, the resting MP was −42.4 ± 2.3 mV, and the conductance was 19.3 ± 4.6 nS. \(I_{\text{inj}}\) made at −60 mV caused cells to depolarize to −30.3 ± 6.5 mV, without significant change in the magnitude of depolarization, immediately after NA and 15 minutes later. However, there was a marked
inhibition of APs after NA, which was gradually reversed within 2 minutes to 59±4.7% of control. Full restoration of APs occurred at 4 minutes (103±5.2%), and enhancement of triggered APs to 150±5.4% of control occurred by 15 minutes (Figure 2B).

In the presence of indomethacin, the resting MP was −45.9±2.7 mV, and the conductance was 20.3±2.6 nS. Inj made at −60 mV caused cells to depolarize to −30.6±7.1 mV without any significant change in the magnitude of depolarization immediately after NA and 15 minutes later. However, the restoration and enhancement of APs were abrogated, and there was a marked inhibition of AP genera-

Figure 1. Effect of mechanical stimulation. A, Responses of 1 neuron to repeated mechanical stimulation at its resting MP of −35 mV. The triggered APs before NA (control) were suppressed immediately after NA (suppressed excitation) and enhanced within 15 minutes (enhanced recovery). B, Bar graph shows that APs generated in the 5 neurons with mechanical stimulation (control) were suppressed immediately after NA and enhanced 15 minutes later. C, Responses from the same neuron (shown in A) but with the MP maintained at −60 mV before and after NA. APs were not triggered during mechanical stimulation at −60 mV, and the depolarizations were not altered significantly by NA. The downward deflections on these tracings refer to measurements of conductances with very brief (100 ms) hyperpolarizing currents. Increases in conductances were noted at the peak depolarizations during mechanical stimulations. The decreases in MP and increases in conductances were not altered significantly (P>0.05) by NA. D, The bar graph shows changes in MP from a fixed −60 mV in 12 neurons in response to mechanical stimulation before (control), immediately after NA, and 15 minutes later. Thus, marked changes in AP generation occurred despite comparable decreases in MP with mechanical stimulation.

Figure 2. Effect of repeated Inj of 1 so on the generation of APs. A, Recordings from a BRN with a resting MP kept at −60 mV in response to 3 Inj show: (1) generation of APs before NA (control); (2) suppression of APs immediately after NA despite a similar ∆MP (middle panel); and (3) recovery with enhancement of APs after 15 minutes in response to the same Inj. B, In 13 neurons, Inj were repeated 8 times after NA to define the pattern of recovery. The group data indicate that recovery of APs was 59±4.7% at 2 minutes, 103±5.2% at 4 minutes, and 150±5.4% at 15 minutes. ∗Significant differences of responses from control at each Inj.

Figure 3. Effect of repeated Inj of 1 so on the generation of APs in presence of 10 μmol/L of indomethacin. A, Recording from 1 neuron shows that suppression of APs that occurs immediately after NA is maintained throughout subsequent Inj over a 15-min period. B, Group data show the marked inhibition of responses to Inj after NA without any evidence of recovery during the subsequent 15 minutes. ∗Significant differences of responses after NA from control at each Inj.
tion, which was sustained for >15 minutes after NA (Figure 3A and 3B).

As a negative control, indomethacin by itself without NA had no significant effect on the generation of APs with $I_{\text{inj}}$ in 2 experiments. Figure 4 shows that $I_{\text{inj}}$ generated 23 spikes/s in 1 neuron before and after 5 minutes in indomethacin (10 μmol/L) and 25 spikes/s after 20 minutes in indomethacin.

Combined Effects of Indomethacin and Exogenous cPGI on Recovery of APs With $I_{\text{inj}}$ After NA

Addition of cPGI to Indomethacin Restored Recovery After NA (Figure 5)

Compared with the effect of indomethacin alone (Figure 3), the following differences were noted as a result of the addition of cPGI (Figure 5). (1) The AP firing was enhanced significantly ($P<0.05$) during control $I_{\text{inj}}$ before NA (26.2±3.1 spikes versus 12.7±2.0 spikes; and (2) APs were suppressed significantly during the first minute after NA, but in contrast to results with indomethacin alone, recovery did occur to ≈50% of control (14.6±5.5 spikes) at 2 minutes and reached a maximum of ≈80% of control (22.6±7.2 spikes) at 4 minutes. There was no further enhancement of AP discharge above control levels between 4 and 15 minutes after NA with indomethacin and cPGI as was the case in the absence of indomethacin (Figure 2).

Generation of PGI₂ in Cultured Nodose Neurons

Results in the Table show that spontaneous generation of PGI₂ was minimal and increased slightly with the addition of arachidonic acid. With electrical field stimulation, PGI₂ increased significantly, and the increase was markedly enhanced with the addition of arachidonic acid and suppressed in the presence of indomethacin.

Discussion

Our goal was to test the hypothesis that neuronal PGI₂ is an important autocrine regulator of baroreceptor nerve activity. The results indicate that: (1) AP responses of isolated aortic BRNs to mechanical stimulation and to 1-s depolarizing $I_{\text{inj}}$ are inhibited after a period of NA; (2) the inhibition involves the loss of APs without a change in the $\Delta V$; (3) recovery of AP generation occurs within 4 minutes after NA and is enhanced by 15 minutes; (4) endogenous neuronal PGI₂ is a major determinant of the recovery because indomethacin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resting</th>
<th>EFS</th>
<th>Arachidonic Acid (10 μmol/L)</th>
<th>Resting</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Indomethacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. 1</td>
<td>10</td>
<td>2200</td>
<td>64</td>
<td>18400</td>
<td></td>
</tr>
<tr>
<td>No. 2</td>
<td>26</td>
<td>943</td>
<td>55</td>
<td>10618</td>
<td></td>
</tr>
<tr>
<td>Indomethacin (10 μmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. 1</td>
<td>12</td>
<td>68</td>
<td>23</td>
<td>1300</td>
<td></td>
</tr>
<tr>
<td>No. 2</td>
<td>10</td>
<td>360</td>
<td>13</td>
<td>1848</td>
<td></td>
</tr>
</tbody>
</table>

Each set of analyses (No. 1 and 2) was carried out on 8 wells, each containing a number of dispersed cells equivalent to those of 1 nodose ganglion in 500 μL.

Results are in pg/100 μL.

EFS indicates electrical field stimulation.
abrogates the recovery and cPGI restores it; and (5) electrical stimulation of nodose neurons in culture generates marked increases in PGI2, which are suppressed by indomethacin.

The discussion addresses the phenomenon of postexcitatory neuronal inhibition and baroreceptor resetting, the selective inhibition of APs while the ΔMP of mechanotransduction is preserved, the possible mechanisms of activation of endogenous PGI2, and a perspective on pathophysiologic implications of the results.

**Postexcitatory Inhibition**

After a 1-minute period of electrical NA with 1-nA current pulses at 20 Hz, tonic BRNs fail to generate repetitive APs transiently. The phenomenon of "postexcitatory inhibition" of baroreceptors has been observed in vivo.5,6 The mechanism varies with different experimental settings. For example, we found that carotid sinus baroreceptors "reset" to a higher pressure threshold after exposure of the sinus to a high distending pressure, and that this resetting is caused in part by activation of Na+/K⁺-ATPase.6 With sustained elevation of nonpulsatile pressure in the carotid sinus, neuronal "adaptation" with suppression of the carotid sinus nerve activity occurs as a result of opening of transient 4-aminopyridine-sensitive potassium channels.25

Also, in renal hypertensive rabbits, the chronic elevation of arterial pressure was accompanied by suppressed carotid BRA and a reduced synthesis of carotid sinus PGI2 from arachidonic acid.13,26,27 These observations, along with the fact that nodose neurons generate endogenous PGI2,19 and prostaglandins activate sensory afferent neurons,10–12,28–34 provided the rationale for the present study and the hypothesis that autocrine PGI2 is an important regulator of BRA.

**Role of PGI2**

Our findings suggest that the generation of endogenous neuronal PGI2 during NA reverses the "postexcitatory inhibition" of APs because indomethacin prolonged the period of inhibition for >15 minutes. This prolonged suppression of APs did not represent a nonspecific loss of responsiveness for 2 reasons: first, there was no inhibition of the depolarizing MP (Figure 3), and second, the addition of cPGI in the presence of indomethacin restored the responsiveness and AP generation with I_in (Figure 5).

In the absence of NA, indomethacin did not reduce the responsiveness of BRN and the APs triggered with I_in (Figure 4). This indicates that neuronal PGI2 may not exert a significant tonic influence on BRNs in the resting state; however, after NA, PGI2 becomes a major determinant of the rescue from "postexcitatory inhibition." This interpretation is supported by our results on the generation of PGI2 in nodose neurons in culture. In unstimulated neurons, PGI2 generation is negligible and increases significantly with electrical activation. This increase is enhanced by an order of magnitude when arachidonic acid is added to the medium, although by itself, in the absence of stimulation, arachidonic acid had only a modest effect. All increases in PGI2 were significantly reduced by indomethacin.

**Selective Inhibition of Mechanically Induced AP Responses and Preservation of Mechanically Induced Depolarizing Receptor Potentials**

The mechanically induced depolarizing receptor potential was not inhibited when the APs were suppressed; nor was it enhanced when APs were enhanced. This selectivity may be explained by the differences in the types of channels mediating these 2 effects. We reported previously that the depolarization potential in aortic BRNs is caused by mechanically gated nongating-gated cationic channels belonging to the degenerin/epithelial Na⁺ channel (DEG/ENaC) family. These mechanosensitive depolarizing channels are blocked by amiloride (a relatively specific blocker of the DEG/ENaC).24,35 and, in contrast to voltage-gated channels, may not be influenced by chemical modulators such as NO or PGI2. Thus, the selectivity of the effect of neuronal PGI2 may relate to the fact that the depolarizing mechanosensitive channels are not voltage gated, and the excitatory action of PGI2 appears to target the voltage-gated Ca2⁺-activated K⁺ channels (most likely Maxi-K⁺ channels) through protein kinase A.22,28

It is possible that Ca2⁺ entry during NA activates NO synthase,8,9 which may decrease BRN activity in part by blocking voltage-gated sodium channels.7 NO may more likely directly activate the constitutive cyclooxygenase-1 (COX-1) than induce COX-2,36–38 resulting in rapid PGI2 generation. Indomethacin inhibits COX-1 and COX-2 with a somewhat greater affinity for COX-1.39

**Possible Action on Other Nonbaroreceptor Nodose Neurons**

We focused on this study on BRNs because of our interest in the phenomenon of resetting of baroreceptors in hypertension. However, resetting of cardiac mechanosensitive vagal afferents has also been reported, and we have seen suppression of neuronal excitability of non-DiI–labeled nodose neurons after NA.40 Therefore, it is possible that other nonbaroreceptor nodose neurons may respond similarly. Furthermore, cardiac vagal afferents, which have their soma in nodose ganglia, do respond to PGI2, and their activation may result in suppression of the arterial baroreflex.12,15 This was an indirect effect of cardiac PGI2 released during coronary occlusion on the baroreflex. In a previous study, we had shown that activation of vagal afferents during coronary ischemia may induce a central interaction, which suppresses the baroreflex.41,42 Conversely, elimination of vagal afferent activity enhances the baroreflex.43

**Relevance of Findings to Resetting of Baroreflex In Vivo**

It is known that arterial baroreceptor sensory endings and the baroreceptor pressure–nerve activity curve can be reset rapidly to a higher pressure, and the pressure threshold increases with even transient elevations of arterial pressure.5–6 This allows the pressure fluctuations around a higher mean arterial pressure to remain on the linear part of the nerve activity curve. It also means that the BRA is less at comparable pressures leading to reflex increases in sympathetic nerve activity, which sustain a hypertensive state. In our isolated
BRN model, a period of 1 minute of NA at 20 Hz simulated the period of transient elevation of arterial pressure, which, in vivo, leads to decreases in activity of baroreceptors over time and their resetting. Our results do indeed show that after NA, the neurons essentially stop generating APs in response to mechanical stimulation and I_{Na}. This decreased neuronal responsiveness could be viewed as the in vivo counterpart of the in vitro resetting. We also report that endogenous neuronal PG12 plays an important autocrine role in restoring the neuronal activity and even enhancing it. An important question is whether PG12 plays a role in the in vivo resetting in hypertensive animals.

We reported previously that indomethacin in the carotid sinus shifts the normotensive BRA curve to the right, bringing it closer to the hypertensive curve, yet it has minimal effect on the curve in the hypertensives. Furthermore, we found that synthesis of PG12 from arachidonic acid was reduced significantly in the carotid sinus of hypertensive animals and therefore concluded that a defect in synthesis of PG12 in the carotid sinus of hypertensive animals contributed to the resetting and the decreased baroreceptor sensitivity.

The results of this study indicate that the origin of released PG12 in the carotid sinus may have been neuronal in addition to endothelial. This conclusion is supported by the observation of Wang et al. that the higher pressure thresholds in the presence of indomethacin were preserved in the absence of the endothelium.

**Perspectives**

Responses to mechanical stimulation in single neurons represent a functional equivalent of stretch of arterial baroreceptors in vivo. The results confirm in vitro that decreased activity or “resetting” of the response to a mechanical stimulus occurs after a period of excessive activation. Our results shed light on possible molecular mechanisms of this “resetting.”

In the isolated neuron, we are able to identify the activation of two types of channels with mechanical stimulation, which we cannot do in vivo with baroreceptor nerves. One is the Δσ, which results from activation of DEG/ENaC mechanosensitive nonvoltage-gated channels. The second is the AP generation through voltage-gated channels. The demonstration that NA causes inhibition of AP generation without inhibiting the mechanically induced depolarization is important. It highlights the channel selectivity of the putative inhibitory mechanism, which causes the shift in threshold and decrease in activity of baroreceptors. It suggests that resetting of hypertensive baroreceptors is not caused by a defective mechanotransduction process and that it could be reversed by activation or blockade of voltage-gated depolarizing or hyperpolarizing channels, respectively. Neuronal PG12 plays a role in this reversal.

Although resting levels of neuronal PG12 may not modulate excitability of the neurons, the amounts generated during neuronal stimulation, especially in the presence of arachidonic acid substrate, are large and capable of reversing the postexcitatory suppression and the “neuronal resetting.” We speculate that a failure of generation of sufficient neuronal PG12 contributes to the impaired baroreceptor sensitivity, which sustains the hypertensive state.

**Acknowledgments**

This publication was made possible by grant number HL14388 from the National Institutes of Health and a VA Merit Review Award to M.W.C. from the Department of Veterans Affairs. The authors wish to thank the College of Pharmacy Cardiovascular Analytical Laboratory, under direction of Dr Bradley G. Phillips, staffed by Donna Farley and Suzan Hays for help in conducting 6-keto PGF1α experiments, Cheryl A. Ridgeway and Mary Ann Boney for typing the manuscript, and Shawn Roach for preparation of the figures.

**References**


Neuronal Prostacyclin Is an Autocrine Regulator of Arterial Baroreceptor Activity
Vladislav Snitsarev, Carol A. Whiteis, Mark W. Chapleau and Francois M. Abboud

Hypertension. published online August 1, 2005;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2005/08/01/01.HYP.0000175475.17666.26.citation

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2006/09/04/01.HYP.0000175475.17666.26.DC1
http://hyper.ahajournals.org/content/suppl/2006/09/03/01.HYP.0000175475.17666.26.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/