Mechanism of Decreased Baroreceptor Activity in Chronic Hypertensive Rabbits

Role of Endogenous Prostanoids

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Abstract

We examined the contribution of endogenous prostanoids to baroreceptor activation in chronic renal hypertension. Baroreceptor activity was recorded from the vascularly isolated carotid sinus during slow ramp increases in pressure in rabbits anesthetized with pentothal and chloralose. Mean arterial pressure averaged 133±4 mmHg in hypertensive rabbits (one kidney, one wrap, n = 12) and 85±3 mmHg in normotensive rabbits (one kidney, no wrap, n = 13). Baroreceptor activity was decreased significantly ($P < 0.05$) in the hypertensive compared with the normotensive rabbits. The decreased baroreceptor activity could not be explained by decreased distensibility of the carotid sinus (sonomicrometers). Inhibition of the endogenous formation of prostanoids with intrasinus administration of indomethacin (50 μM) decreased baroreceptor activity in normotensive ($P < 0.05$) but not in hypertensive rabbits over a wide range of pressures. At a pressure of 120 mmHg, activity declined from 61±14 spikes/s before indomethacin to 47±12 spikes/s with indomethacin, i.e., a drop of 24±4%. In contrast, corresponding values in hypertensive rabbits averaged 41±13 and 40±12 spikes/s (−1±2%). Intrasinus prostacyclin, on the other hand, increased activity in both groups: at 120 mmHg activity increased from 62±9 to 92±15 spikes/s (51±17%) in normotensive rabbits and from 29±7 to 47±14 spikes/s (68±23%) in hypertensive rabbits. Neither indomethacin nor prostacyclin (n = 5) influenced the pressure–diameter relation of the carotid sinus. The increase in prostacyclin (6-keto-$PGF_{1\alpha}$) formation by the sinus in response to its exposure to arachidonic acid (10 μM) was significant ($P < 0.05$) in the normotensives (1,627±344%; n = 5) but not in the hypertensives (583±353%; n = 5). We conclude that the decreased baroreceptor activity in chronic hypertension may not be caused by decreased distensibility of the vascular wall of the sinus and that endogenous prostanoids that contribute to baroreceptor activation in normotensive rabbits fail to do so in hypertensive rabbits. This appears to be due to decreased formation of prostacyclin rather than decreased sensitivity of the baroreceptors to prostacyclin. The results suggest a new mechanism that contributes to chronic baroreceptor resetting in hypertension. (*J. Clin. Invest.* 1990. 86:625–630.) Key words: baroreceptor resetting • prostacyclin • carotid sinus • endothelium • high blood pressure

Introduction

In chronic hypertension the arterial baroreceptors are reset to operate at higher levels of arterial pressure with less nerve activity at equivalent levels of pressure compared with that in normotensive animals (1–7). Chronic resetting of baroreceptors has often been attributed to decreased vascular distensibility and less stretch of baroreceptor endings in hypertensive animals (1, 2).

Recent studies in our laboratory have demonstrated that prostanoids, e.g., prostacyclin (PGI_2),[1] released from the endothelium during vascular stretch, contribute to the activation of baroreceptors (8) and enhance the baroreflex inhibition of lumbar sympathetic nerve activity (9). In chronic hypertension there are morphological alterations in arterial endothelial cells (10), and PGI_2 production by the endothelium may be impaired (11–18).

Based on these studies we hypothesized that impaired production of prostanoids may contribute to chronic resetting and decreased baroreceptor activity in chronic hypertensive states. Specifically, we addressed the following questions. (*a*) Can chronic resetting and decreased baroreceptor activity in renal hypertensive rabbits be explained totally by decreased vascular distensibility? (*b*) If not, do endogenous prostanoids released from the carotid sinus contribute to activation of baroreceptors in the hypertensive rabbits; i.e., does indomethacin suppress activity in hypertensive rabbits as it does in normotensive rabbits? (*c*) If endogenous prostanoids do not contribute to baroreceptor activation in hypertensive rabbits, is it because of an inability of baroreceptors to respond to prostanoids or because of impaired production of prostanoids?

Methods

New Zealand white rabbits (3–4 lb) of either sex were anesthetized with ketamine (Ketalar; Park-Davis, Morris Plains, NJ) (40 mg/kg i.m.) and acetylpromazine (Acepromazine; Tech America, Elwood, KS) (1 mg/kg i.m.). Hypertension was induced in 12 rabbits by removing one kidney and wrapping the other in dialysis membrane (19) using sterile surgical technique. 13 other rabbits had one kidney removed and the other kidney exposed but not wrapped and served as the normotensive controls. Arterial pressure was measured noninvasively in the conscious rabbit each week postoperatively with a Grant-Rothschild capsule (20). Pressure increased from ~ 80 to > 100 mmHg within 4–13 wk after surgery in the hypertensive group.

1. *Abbreviation used in this paper:* PGI_2, prostacyclin.

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The rabbits were anesthetized with thiopental sodium (25–30 mg/kg i.v.) and chloralose (100 mg/kg i.v.) 10–24 wk after surgery, and 3–16 wk after the animals became hypertensive (pressure > 100 mmHg). A tracheotomy was performed and the animals were mechanically ventilated with a mixture of room air and 100% oxygen. Catheters were placed in the femoral artery and vein for measurement of arterial pressure and administration of anesthetic, respectively. To eliminate skeletal muscle contraction, gallamine triethiodide (1 mg/kg i.v.) was administered before recording nerve activity. Supplemental doses of chloralose and gallamine were given as needed. All procedures followed were in accordance with institutional guidelines.

Isolated carotid sinus preparation

One carotid sinus was vascularly isolated as described previously (8, 9). All visible branches of the common and external carotid arteries were ligated. Catheters were positioned in the common and external carotid arteries and the internal carotid artery was ligated. The sinus region was filled with a physiological saline solution of the following composition (in mM): NaCl 98.0, KCl 4.7, $NaHCO_3$ 24.0, KH_2PO_4 1.1, $MgSO_4$ 1.2, CH_3COONa 20.0, $CaCl_2$ 2.5, and glucose 10.0. The solution was equilibrated with a 95% O_2, 5% CO_2 gas mixture (Po_2 > 200 mmHg, Pco_2 = 25–40 mmHg, pH = 7.3–7.4) and warmed to 37°C in a water jacket before use. The carotid sinus was periodically refilled with fresh saline solution. The common carotid catheter was connected to a pressure bottle filled with the physiological saline, and carotid sinus pressure was controlled by regulating the inflow of air to the bottle from a pressurized air source. Carotid sinus pressure was measured with a pressure transducer (model P23Ia; Statham, Hato Rey, PR) connected to the external carotid catheter.

Measurement of carotid sinus nerve activity

Baroreceptor activity was measured as described previously (8, 21) and is described briefly. The vagus, aortic, and cervical sympathetic nerves were cut caudal to the carotid sinus. The sinus nerve was identified, cut, and placed on bipolar platinum electrodes. The nerve and electrodes were encased in Wacker Sil-Gel (22) and the sinus region was bathed externally with physiological saline. Carotid sinus nerve activity was recorded using a high-impedance probe (model HIP511E; Grass Instrument Co., Quincy, MA) and a preamplifier (model P511; 30 Hz to 3–10 kHz bandwidth; Grass Instrument Co.). The electroneurogram was displayed on an oscilloscope (model 5113; Tektronix, Inc., Beaverton, OR) and monitored with a loudspeaker. A nerve traffic analyzer (model 605C; University of Iowa Bioengineering, Iowa City, IA) counted action potentials that exceeded a selected voltage. To assure selective measurement of pressure-sensitive baroreceptor activity, the voltage level or window was routinely placed just above the baseline nerve activity that was sometimes present at very low carotid sinus pressures (0–20 mmHg). Measurement of nerve activity and systemic and carotid sinus pressures were displayed on a chart recorder (model 3414; Soltec Corp., Sun Valley, CA).

Measurement of carotid sinus diameter

The diameter of the carotid sinus was measured with sonomicrometer crystals (8, 21, 23, 24). A low resistance stainless steel clip holding two miniature piezoelectric crystals (5 mHz) was placed across the carotid sinus and sutured to the adventitia (8, 21). The diameter of the sinus was determined from the transit time of acoustic signals between the crystals.

Drugs

Indomethacin (Sigma Chemical Co., St. Louis, MO) was dissolved in physiological saline with Na_2CO_3 in a ratio of 2:1. PGI_2 (Sigma Chemical Co.) was dissolved in 50 mM $NaHCO_3$, separated into small aliquots (50–100 μl), lyophilized, and kept at −70°C until ready for use. Arachidonic acid (NuCheck Prep, Inc., Elysian, MN) was prepared in dimethylsulfoxide, separated into 100-μl aliquots, and kept at −70°C. All drugs were diluted to the desired concentration with physiological saline just before use.

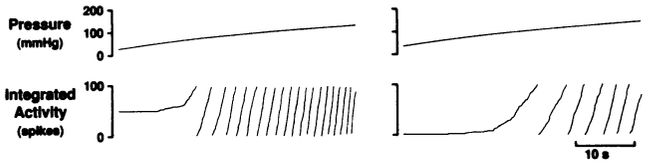

Figure 1. Baroreceptor responses in a normotensive and a hypertensive rabbit. Shown are original tracings of pressure in the isolated carotid sinus and integrated carotid sinus nerve activity obtained from a normotensive (*left*) and a hypertensive (*right*) rabbit. Nerve activity began to increase at a much lower pressure and the level of activity (slope of the integrated activity record) was much greater in the normotensive compared with the hypertensive rabbit.

Measurement of PGI_2 production

PGI_2 production by the isolated carotid sinus was determined by measuring the concentration of the stable metabolic breakdown product of PGI_2, 6-keto-$PGF_{1\alpha}$ (radioimmunoassay) (25) in 100-μl samples of saline solution withdrawn from the isolated sinus. The samples were frozen at −70°C until the time of assay.

Protocols

Pressure–baroreceptor activity relation. Baroreceptor activity was recorded during slow ramp increases (2–4 mmHg/s) in nonpulsatile pressure in the isolated carotid sinus from 0 to 150 mmHg in normotensive (n = 8) and hypertensive (n = 9) rabbits. Before each ramp, carotid sinus pressure was held for at least 10–15 min at the level of mean arterial pressure recorded directly through a catheter placed either in a central ear artery in the conscious rabbit before administration of anesthetics or in a femoral artery after pentothal anesthesia.

The baroreceptor responses to ramp increases in pressure were also obtained before and during exposure to 10 μM PGI_2, (normotensive, n = 5; hypertensive, n = 5). PGI_2 was placed inside and around the carotid sinus ~ 8 and again 1–2 min before the pressure ramp was applied. PGI_2 was removed from the carotid sinus by thoroughly

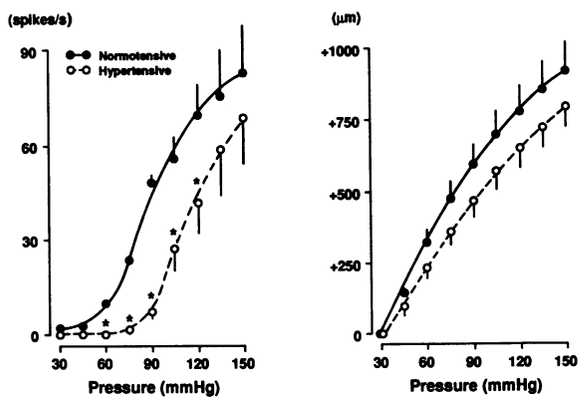

Figure 2. Average levels (±SE) of baroreceptor activity (*left*) and carotid sinus diameter (*right*) that occurred in response to increases in carotid sinus pressure. The pressure–nerve activity relation was shifted to the right with significantly less activity (*P < 0.05) over a wide range of carotid sinus pressures in the hypertensive (n = 9) compared with the normotensive (n = 8) rabbits. There was no significant difference in the pressure–diameter relations of the carotid sinus in the normotensive (n = 5) vs. the hypertensive (n = 5) rabbits. The baseline diameter measured at a pressure of 30 mmHg was significantly larger in the hypertensive vs. the normotensive rabbits, averaging 1,686±68 and 1,431±52 μm, respectively.

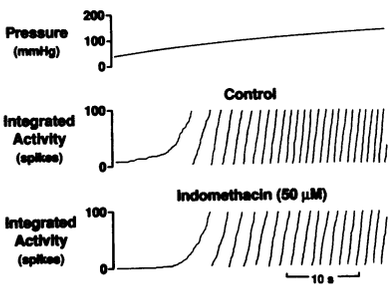

Figure 3. Decreased baroreceptor activity with 50 μM indomethacin in a normotensive rabbit. The two pressure ramps applied before and during exposure of the carotid sinus to indomethacin were identical and only one ramp is shown here for clarity.

flushing the inside and outside of the sinus with physiological saline, and recovery responses to the pressure ramp were then obtained.

The baroreceptor responses to increased pressure were also obtained before and during exposure to 50 μM indomethacin (normotensive, $n = 7$; hypertensive, $n = 7$). The isolated sinus was exposed to indomethacin for 10–15 min before the ramp was applied.

Pressure–diameter relation. The diameter of the carotid sinus was recorded during slow ramp increases (2–4 mmHg/s) in nonpulsatile carotid sinus pressure in normotensive ($n = 5$) and hypertensive ($n = 5$) rabbits. The effects of PGI_2 and indomethacin on the pressure–diameter relation of the carotid sinus were determined as described above for the nerve recording experiments. In two of the five hypertensive rabbits, both diameter and nerve activity were recorded.

PGI_2 production by the isolated carotid sinus. The rate of formation of PGI_2 by the isolated carotid sinus was determined in the same five normotensive and five hypertensive rabbits in which carotid sinus diameter was measured. The carotid sinus was flushed with saline and pressure was held at 10 mmHg for 10 min, after which a 100-μl sample of saline solution was withdrawn from the sinus. This control sample was frozen at −70°C and assayed at a later time for 6-keto-$PGF_{1\alpha}$. The rate of formation of PGI_2 was calculated and expressed in picograms per milliliter per minute of 6-keto-$PGF_{1\alpha}$ formed. The capacity to increase PGI_2 was evaluated by measuring 6-keto-$PGF_{1\alpha}$ formation after a 10-min exposure of the isolated carotid sinus to 10 μM arachidonic acid. PGI_2 formation was also determined before and during exposure to arachidonic acid in the presence of 50 μM indomethacin.

Data analysis

The absolute level of baroreceptor activity and increases in carotid sinus diameter were plotted as a function of increases in carotid sinus pressure. The influence of hypertension and the effects of indomethacin and PGI_2 on baroreceptor activity and carotid sinus diameter were determined with comparisons at equivalent levels of pressure. The baseline levels of PGI_2 formation and the percent increases in PGI_2 formation in response to stimulation with arachidonic acid were compared in normotensive and hypertensive rabbits. The influence of drug treatment was evaluated with the paired t test (26) and all responses in normotensive vs. hypertensive rabbits were compared with the unpaired t test (26). All values represent means±SE. Statistical significance was defined at $P < 0.05$.

Results

Mean arterial pressure averaged 133±4 mmHg in renal hypertensive rabbits ($n = 12$) and 85±3 mmHg in sham-operated normotensive rabbits ($n = 13$). Baroreceptor activity was significantly less in the hypertensive rabbits than in the normotensive rabbits over a wide range of carotid sinus pressures (Figs. 1 and 2).

The diameter at a distending pressure of 30 mmHg was greater ($P < 0.05$) in the hypertensive (1,686±68 μm) than in the normotensive (1,431±52 μm) group, but the distensibility of the carotid sinus (i.e., the increase in diameter during the increase in distending pressure) tended to be less in the hypertensives, and the difference between the two groups was not significant (Fig. 2).

Intrasinus indomethacin decreased baroreceptor activity significantly over a wide range of pressure in normotensive rabbits (Figs. 3 and 4). The maximal decrease occurred at a pressure of 120 mmHg from 61±14 to 47±12 spikes/s (−24±4%). In contrast, indomethacin did not influence activity significantly in hypertensive rabbits (Fig. 4); activity averaged 41±13 and 40±12 spikes/s (−1±2%) at 120 mmHg before and during indomethacin, respectively.

Intrasinus PGI_2 increased baroreceptor activity significantly in both normotensive and hypertensive animals (Figs. 5 and 6). PGI_2 increased baroreceptor activity at 120 mmHg from 62±9 to 92±15 spikes/s (51±17%) in normotensive rabbits and from 29±7 to 47±14 spikes/s (68±23%) in hypertensive rabbits. The sensitization of baroreceptors was readily reversed upon removal of PGI_2 from the carotid sinus; activity at a pressure of 120 mmHg returned to an average of 45±3 and 29±11 spikes/s in normotensive and hypertensive rabbits, respectively.

At a high carotid sinus pressure of 150 mmHg indomethacin reduced baroreceptor activity in normotensive rabbits to

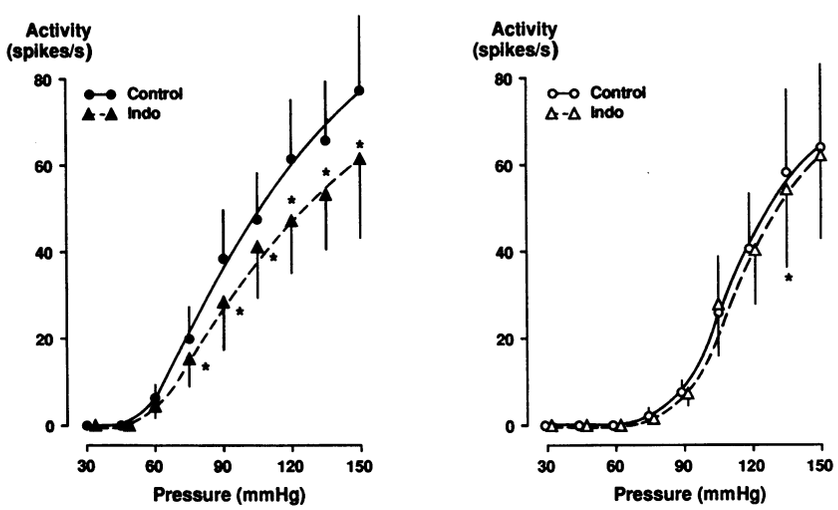

Figure 4. The group results summarizing the effects of 50 μM indomethacin on baroreceptor activity in normotensive ($n = 7$, *left*) and hypertensive ($n = 7$, *right*) rabbits. Indomethacin decreased baroreceptor activity significantly (*$P < 0.05$) over a wide range of pressure in normotensive rabbits, but generally failed to reduce activity in hypertensive rabbits.

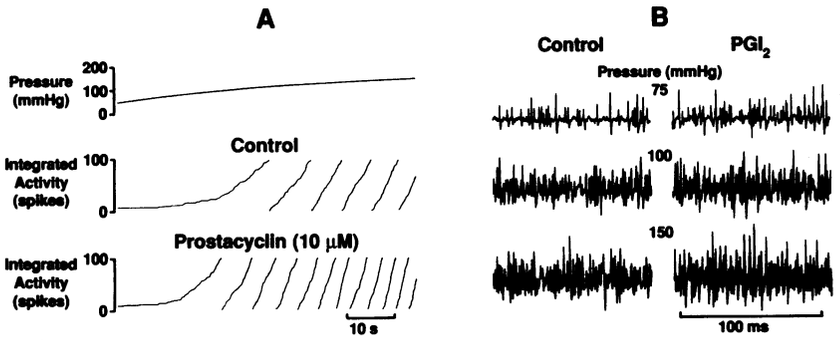

Figure 5. Effect of 10 μM PGI_2 on baroreceptor activity in a hypertensive rabbit. The increases in nerve activity recorded during ramp increases in carotid sinus pressure before and during PGI_2 are shown in *A*. The neurograms recorded in this experiment in the absence (control) and presence of PGI_2 at 75, 100, and 150 mmHg are shown in *B* at a faster paper speed. Baroreceptor activity was increased in the presence of PGI_2.

levels not significantly different from those in hypertensive rabbits, and PGI_2 increased activity in hypertensive rabbits to levels not different from those in normotensive rabbits (Figs. 4 and 6).

Neither indomethacin nor PGI_2 altered the carotid sinus pressure–diameter relation in normotensive and hypertensive rabbits (Fig. 7).

The baseline production of PGI_2 was higher in the hypertensive rabbits (425±96 pg/ml per min, 6-keto-$PGF_{1\alpha}$; n = 5) compared with the normotensive rabbits (184±61 pg/ml per min; n = 5). Intrasinus administration of arachidonic acid increased PGI_2 formation significantly more ($P < 0.05$) in the normotensive (1,627±344%) than in the hypertensive (583±353%) rabbits. In the presence of indomethacin, arachidonic acid failed to increase PGI_2 formation in normotensive (1±36%) and hypertensive (23±55%) rabbits.

Discussion

The principal findings in this study were: (*a*) There is a marked decrease in carotid baroreceptor activity in renal hypertensive rabbits, which is not explained by changes in carotid distensibility. (*b*) Inhibition of the formation of endogenous prostanoids with indomethacin, which suppresses baroreceptor activity in normotensive rabbits (8), does not suppress activity in renal hypertensive rabbits. Thus, endogenous prostanoids contribute to baroreceptor activation in normotensive rabbits but fail to do so in hypertensive rabbits. (*c*) Exogenous PGI_2 increases baroreceptor activity to a similar extent in normotensive and hypertensive rabbits, suggesting that baroreceptors maintain their responsiveness to prostanoids in hypertension and that absence of an effect of indomethacin in hypertension may be caused by decreased formation of prostanoids. (*d*) These effects of indomethacin and PGI_2 are not caused by changes in compliance of the carotid sinus. (*e*) There is a decreased capacity of the carotid sinus in hypertensive rabbits to increase PGI_2 formation in response to arachidonic acid.

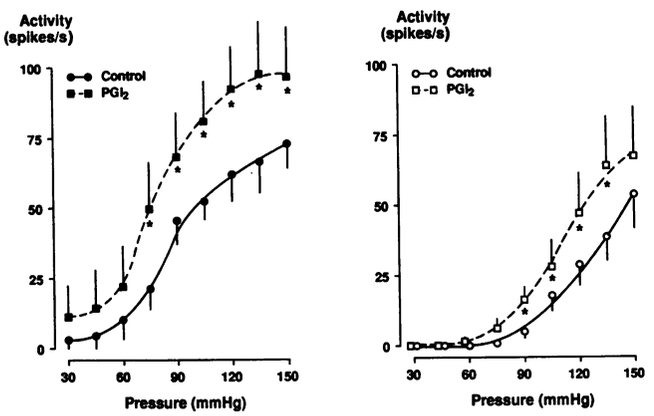

Figure 6. The group results summarizing the effects of 10 μM PGI_2 on baroreceptor activity in normotensive (n = 5, *left*) and hypertensive (n = 5, *right*) rabbits. PGI_2 increased baroreceptor activity significantly (*$P < 0.05$) over a wide range of pressure in both normotensive and hypertensive rabbits.

Mechanisms of chronic baroreceptor resetting in hypertension. Baroreceptors are reset in chronic hypertension with less nerve activity at equivalent levels of arterial pressure compared with that in normotensive animals (1–7). The decreased baroreceptor activity may contribute to the maintenance of the hypertension. The mechanisms responsible for chronic baroreceptor resetting are not completely understood (3).

It has been proposed that structural changes caused by chronic hypertension are responsible for the decreased baroreceptor activity (1, 2). Vascular hypertrophy and decreased distensibility may reduce the deformation of baroreceptor nerve endings and decrease nerve activity (1, 2). Other studies have shown that the decreased baroreceptor activity cannot be entirely explained by decreased vascular distensibility with several reports of significant resetting of baroreceptors despite normal distensibility and wall strain (5–7). Decreased strain sensitivity has been ascribed in these experiments to ionic mechanisms (2, 5, 6) that also contribute to resetting of baroreceptors during acute hypertension (3, 27, 28).

The decreased baroreceptor activity in the renal hypertensive rabbits in our experiments cannot be explained by changes in the mechanical characteristics of the vascular wall. First, the diameter was significantly greater in the hypertensives at 30 mmHg; i.e., the wall strain was greater, yet the threshold pressure needed to activate baroreceptors was higher in the hypertensives (Fig. 2). Second, the increase in diameter with the rise in distending pressure (i.e., the distensibility of the sinus) was not significantly different in the two groups. Third, exposure of the carotid sinus of the hypertensive rabbits to PGI_2 increased nerve activity to levels similar to those recorded in the normotensive rabbits (Fig. 6). Fourth, exposure to indomethacin decreased activity in normotensives to levels seen in hypertensives (Fig. 4).

The present results suggest that a loss of the excitatory influence of endogenous prostanoids is a possible mechanism of the decreased strain-sensitivity of baroreceptors in chronic hypertension.

Alterations in prostanoid production in hypertension. There is abundant evidence of altered production of prostanoids in

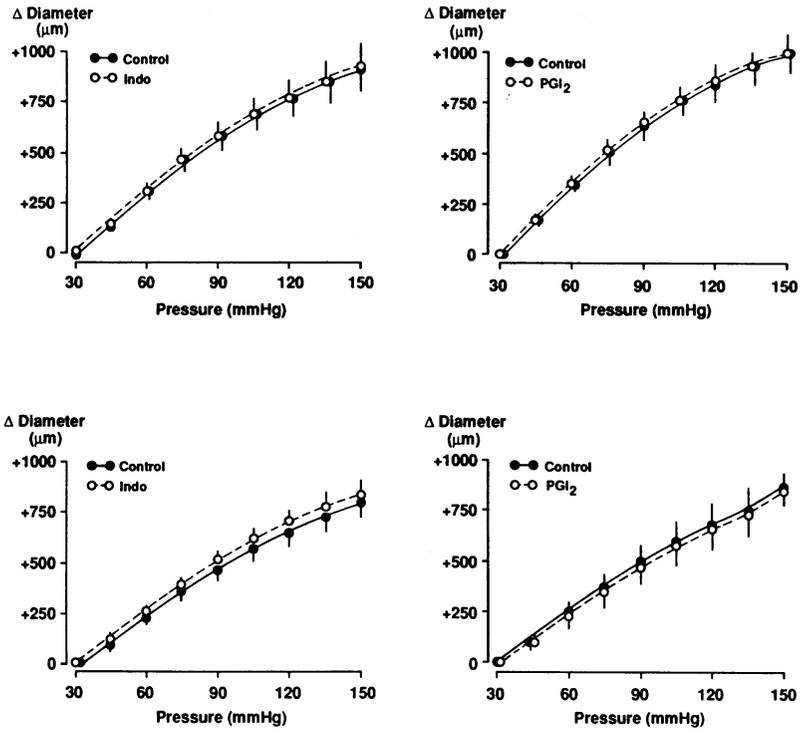

Figure 7. Lack of effect of indomethacin and PGI_2 on the pressure–diameter relation of the isolated carotid sinus. Neither 50 μM indomethacin (*Indo*, $n = 5$) nor 10 μM PGI_2 ($n = 5$) altered the pressure–diameter relation in normotensive (*top*) and hypertensive (*bottom*) rabbits. The baseline diameter measured at a pressure of 30 mmHg was significantly larger ($P < 0.05$) in the hypertensive vs. the normotensive rabbits averaging 1,686±68 and 1,439±48 μm, respectively, in the indomethacin experiments and 1,697±95 and 1,468±51 μm, respectively, in the PGI_2 experiments.

chronic hypertension (11–18, 29–31). Prostanoid production by the kidney (12, 17, 18), by the perfused mesenteric vascular bed (13), and the 24-h urinary excretion of endogenous metabolites of PGI_2 (11, 12) are impaired in various animal models of hypertension. In addition, the increase in PGI_2 production by blood vessels in response to various neurohumoral or chemical stimuli is impaired in hypertensive animals (14–16). It is interesting that the impaired formation of prostanoids may be apparent before the development of hypertension (29), suggesting that the impairment may contribute to the pathogenesis of hypertension.

In contrast, several studies in vitro indicate that the production of prostanoids is not reduced but augmented in hypertensive animals (15, 29–31). Our finding of increased basal release of PGI_2 from the carotid sinus of hypertensive rabbits is in agreement with these in vitro studies.

Why might basal production of PGI_2 in the carotid sinus be augmented in hypertension? First, increased PGI_2 production in vitro is associated with increased PGI_2 synthase activity in the vascular wall (29), which may be a compensatory response to factors in vivo, such as a circulating factor, that may inhibit prostanoid production (11, 12), e.g., through inhibition of phospholipase. Second, if there is vascular hypertrophy the increased wall mass may explain in part the increased PGI_2 production. The enhanced prostanoid production observed by others (15, 29–31) occurred after the development of hypertension. An important consideration is the source within the vascular wall of prostanoids that activate baroreceptors. The endothelium is considered the primary vascular source of prostanoid formation (32, 33). Smooth muscle cells may also produce PGI_2, but in contrast to endothelial cells, are severely limited in their ability to increase PGI_2 production in response to acute stimuli such as arachidonic acid or calcium ionophore (34). In hypertension, the basal levels of PGI_2 production may be maintained or even increased as a result of increased activity of PGI_2 synthase (29), which is normally present in similar concentrations in both endothelium and smooth muscle (33). In contrast, PGI_2 formation in response to an acute stimulus such as increased arterial pressure may be impaired because of morphological and functional alterations in endothelial cells (10). The intrinsic defect in hypertension may be decreased phospholipase activity (29) and reduced availability of free arachidonic acid (13) during vascular stretch, or decreased activity of PGH synthase (a component of cyclooxygenase), which is primarily present in endothelium and not in smooth muscle (33).

Role of endothelium in baroreceptor activation. The results confirm our previous findings that a prostanoid released during vascular stretch contributes in a paracrine manner to the activation of baroreceptors in normotensive animals (8, 9). We believe the endothelium is the primary source of the prostanoids. Endothelial cells possess ion channels sensitive to stretch (35) and produce PGI_2 during acute increases in arterial pressure and vascular stretch (36, 37). In chronic hypertension, the production of PGI_2 in response to acute increases in pressure may be impaired. The loss of the excitatory influence of prostanoids on baroreceptors may contribute to chronic resetting of baroreceptors in hypertension.

In addition, we have recently demonstrated the release of an "inhibitory factor" from cultured endothelial cells that suppresses baroreceptor activity (21). The potential role of this "inhibitory factor" in chronic baroreceptor resetting remains to be determined.

Acknowledgments

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