Chronic Converting Enzyme Inhibition Facilitates Baroreceptor Resetting to Hypertensive Levels

Valdo J. Dias da Silva, Soraia Vargas da Silva, Maria Cristina O. Salgado, Hélio C. Salgado

Abstract

We investigated the acute and chronic effects of converting enzyme inhibitors (captopril or enalapril) and of angiotensin II receptor blockade (DuP 753) on rapid (30-minute) baroreceptor resetting elicited by a prompt and sustained hypertensive response provoked by aortic constriction. Pressure-nerve activity curves, pressure at 50% of maximal baroreceptor activity, baroreceptor gain (slope of the curve), and systolic threshold pressure for baroreceptor activation were determined as indexes of baroreceptor function. A slight fall in mean arterial pressure after acute treatment with the converting enzyme inhibitor or DuP 753 was accompanied by a partial leftward curve shift, which is associated with a partial threshold shift and increase in gain. A maintained hypertensive stimulus caused a partial rightward curve shift and partial (49% to 56%) threshold shift to hypertensive levels in both acutely treated and control rats. The hypertensive stimulus provoked a partial rightward curve shift and complete (88% to 94%) threshold shift to hypertensive levels in chronically treated rats. The effect of enalapril on baroreceptor function was unaltered by the bradykinin antagonist Hoe 140. These data demonstrate that chronic inhibition of converting enzyme or blockade of angiotensin II receptors facilitates rapid resetting of the baroreceptors to hypertensive levels caused by partial aortic constriction without a change in baroreceptor sensitivity. (Hypertension. 1994;23[suppl I]:I-68-I-72.)

Key Words • captopril • enalapril • pressoreceptors • losartan • angiotensin converting enzyme inhibitors

Angiotensin converting enzyme (ACE) inhibition and baroreceptor reflex function have been extensively studied both clinically and experimentally. An augmentation of baroreceptor reflex function after chronic ACE inhibition has been observed in patients as well as in experimental animals, but the primary site of action where ACE inhibition improves baroreceptor reflex function, the afferent (baroreceptor activity) or central level, is not yet firmly established. Various antihypertensive drugs modulate rapid baroreceptor resetting to hypertensive levels, and among these, long-term (7-day) blockade of angiotensin II (Ang II) generation with captopril most efficiently modulates rapid resetting. Vasoactive peptides such as Ang II also affect baroreceptor function. Experiments in vitro in an aortic arch preparation have demonstrated that as Ang II concentration increases, the pressure-nerve activity curves shift in a parallel manner to higher pressures, requiring a substantially higher pressure threshold for baroreceptor activation. Accordingly, endogenous vasoactive peptides such as Ang II might also modulate rapid resetting. Changes in pressure threshold are linearly related to changes in conditioning pressure over a wide range, and rapid resetting is usually recognized as partial because the magnitude of the shift in pressure threshold is approximately 50% or less of the magnitude of change in conditioning pressure. Nevertheless, when rapid resetting was driven to hypertensive levels with the conditioning pressure under the influence of an antihypertensive agent, the baroreceptors totally adapted within 15 minutes.

To our knowledge the effect of ACE inhibition on rapid baroreceptor resetting has not yet been investigated in any hypertensive model. Therefore, we evaluated in the present study the extent of rapid (30-minute) resetting elicited by a prompt and sustained rise in arterial pressure in normotensive rats treated acutely (15 minutes) or chronically (7 days) with ACE inhibitors, captopril or enalapril, and an AT1 receptor antagonist, DuP 753. We also investigated the role played by bradykinin potentiation on rapid baroreceptor resetting during blockade of ACE.

Methods

Experiments were performed on anesthetized (thiopental sodium, 40 mg/kg IP) normotensive male Wistar rats (250 to 300 g) in accordance with the guiding principles of the American Physiological Society. Catheters were placed into the right common carotid artery for measurement of arterial pressure, the right femoral artery for withdrawal and reinfusion of blood, and the right femoral vein for the administration of drugs. A pneumatic cuff was placed around the abdominal aorta immediately below the diaphragm to produce a prompt and sustained hypertensive stimulus for baroreceptor activation.

The procedure for recording the whole-nerve activity of the aortic baroreceptor was the same as that used in previous studies, with some modifications. Briefly, the left aortic nerve was isolated and supported by a bipolar stainless steel electrode and carefully insulated with silicone rubber (Wacker sil gel 604, Wacker Co, Munich, FRG). Carotid pressure was recorded simultaneously with aortic nerve discharges on an oscilloscope (model 5113, Tektronix, Beaverton, Ore) and monitored with a loudspeaker. A nerve traffic analyzer (model 605C, University of Iowa Bioengineering, Iowa City) counted action potentials that exceeded a selected voltage. The nerve traffic analyzer was set to operate in “rate” mode, acting as an instantaneous frequency meter operating with a full scale of 1000 Hz and time constant of 0.2 second in all experiments. The output (spikes per second) from the traffic analyzer and
carotid pressure were recorded continuously on a two-channel chart recorder (Narco trace 40, Narco BioSystems, Houston, Tex). For determination of the baroreceptor firing range, rats were submitted to rapid (20- to 30-second) changes in arterial pressure by withdrawal and reinfusion of blood into the femoral artery. To avoid the influence of hysteresis, we used only the values obtained during reinfusion of blood when pressure increased (rate approximately 2 to 3 mm Hg/s). The systolic threshold pressure (SPth) for baroreceptor activation and the pressure-nerve activity curve were determined. Aortic nerve activity (spikes per second) was analyzed in relative units (percent of maximum activity). Normalized baroreceptor activity was plotted against mean arterial pressure (MAP) to obtain pressure-nerve activity curves. The pressure at 50% of maximal activity (MAPₚₐ) and the baroreceptor gain (slope of the linear portion of the curves) were calculated. The indexes used to evaluate the extent of rapid resetting of the baroreceptors were the ratios of (ΔSPth/ΔCDP) × 100, where CDP is control diastolic pressure, and (ΔMAPₚₐ/ΔMAP) × 100, which defines the shift of the entire pressure-nerve activity curve during rapid resetting.

**Experimental Protocol**

**Acute Treatment**

Fifteen minutes after baroreceptor activity was recorded, normotensive rats received an intravenous bolus of captopril (10 mg/kg, n=7), enalapril (5 mg/kg, n=7), or DuP 753 (10 mg/kg, n=6). Fifteen minutes after treatment, aortic baroreceptor activity was recorded again. Rats were then submitted to a prompt and sustained (30-minute) increase in MAP by means of aortic constriction. Ten normotensive rats treated with saline and submitted to the hypertensive stimulus were used as controls. In this protocol the extent of resetting was measured 15 minutes after treatment as well as 30 minutes after the hypertensive stimulus.

**Chronic Treatment**

Normotensive rats were chronically treated during 7 days with captopril (30 mg/kg per day, n=7), enalapril (20 mg/kg per day, n=7), or DuP 753 (3 mg/kg per day, n=7) (all administered once daily orally) or enalapril plus Hoe 140 (500 μg/kg per day SC using Alzet 2001 osmotic minipumps, Alza Corp, Palo Alto, Calif; n=8). On the day of experiment, aortic baroreceptor activity was recorded, and the animals were submitted to the hypertensive stimulus during 30 minutes. At the end of this period, the aortic nerve activity was recorded again. In this protocol the extent of resetting was measured only 30 minutes after the hypertensive stimulus.

Tests with angiotensin I (Ang I) (100 ng/kg IV bolus), Ang II (100 ng/kg IV bolus), and bradykinin (250 ng IA bolus) were performed before (acute protocol only) and after treatment with captopril, enalapril, enalapril plus Hoe 140, or DuP 753 to determine the effectiveness of these blockers. Captopril was obtained from ER Squibb & Sons, Princeton, NJ; enalapril from Merck Sharp & Dohme Research Laboratory, Rahway, NJ; DuP 753 from Du Pont, Wilmington, Del; and Hoe 140 from Hoechst AG, Frankfurt, FRG. All peptides were purchased from Sigma Chemical Co, St Louis, Mo.

**Data Analysis**

Baroreceptor activity was expressed as a percent of maximum activity obtained during the increase in pressure. The slope of the linear portion of the pressure-nerve activity curve over the pressure range of 50 to 150 mm Hg was calculated with linear regression analysis. The Student’s paired t test was used to determine whether the extent of resetting within each group was partial or total. Resetting was considered partial (not complete) when the magnitude of the shift in SPth (or MAPₚₐ) differed significantly from the magnitude of the change in CDP (or MAP); otherwise, resetting was considered total (complete). Slopes and the extents of resetting were compared among groups with one-way analysis of variance and the Student’s unpaired t test. Analysis of variance with Bonferroni’s multiple comparisons test was used to compare the effects of changes in holding pressure within each group. Changes were considered statistically significant at a value of P<.05.

**Results**

The effects of a rapid and sustained hypertensive stimulus on baroreceptor activity in control rats and rats acutely treated with captopril, enalapril, or DuP 753 are presented in Fig 1. Numerical results are given as mean±SEM. In control rats an increase in MAP of 39±4 mm Hg (basal MAP of 111±2 mm Hg) caused a rightward curve shift (58±9%) without change in baroreceptor gain. A partial (52±5%) threshold shift of the baroreceptors to hypertensive levels was observed. The acute blockade of Ang II elicited by itself a slight but significant fall in MAP (16±6, 10±2, and 10±1 mm Hg, respectively, with captopril, enalapril, and DuP 753). The fall in MAP promoted a leftward shift and partial (77±17%, 59±10%, and 48±7%, respectively, for captopril, enalapril, and DuP 753) threshold shift of the baroreceptors associated with a significant increase in baroreceptor gain. Aortic constriction produced a similar increase in MAP in treated rats (47±6, 42±3, and 47±4 mm Hg, respectively). This prompt and sustained hypertensive stimulus caused a rightward curve shift in treated rats (64±3%, 63±4%, and 51±4%, respectively) and partial (55±5%, 49±5%, and 56±3%, respectively) threshold shift of the baroreceptors without change in gain.

The effect of the hypertensive stimulus on baroreceptor activity in rats chronically treated with ACE inhibitors or DuP 753 is shown in Fig 2. Aortic constriction also caused a similar increase in MAP (43±3, 34±3, 42±5, and 35±2 mm Hg, respectively, for captopril, enalapril, enalapril plus Hoe 140, and DuP 753). The hypertensive stimulus caused a rightward curve shift (87±7%, 91±8%, 96±7%, and 87±1%, respectively) and total (92±3%, 94±4%, 88±2%, and 89±2%, respectively) threshold shift of the baroreceptors without change in gain.

**Discussion**

We investigated the effect of acute or chronic ACE inhibition and blockade of AT₁ receptors on rapid resetting elicited by means of a prompt and sustained hypertensive stimulus caused by aortic constriction. Normotensive rats treated acutely with captopril, enalapril, or DuP 753 presented a slight but significant fall in MAP associated with a partial leftward curve shift and partial threshold shift to hypertensive levels. These data confirm previous observations from our laboratory, based on changes of systolic pressure threshold for baroreceptor activation, that acute ACE inhibition with captopril facilitates rapid resetting to hypertensive levels. Nevertheless, the present study also demonstrates that acute ACE inhibition or blockade of Ang II receptors increases baroreceptor sensitivity. A prompt and sustained hypertensive stimulus promoted a rightward curve shift in the acutely treated rats associated with a
Fig 1. Plots show pressure-nerve activity curves expressed as percentage of maximal activity vs mean arterial pressure using a regression curve obtained from coefficients of third-order polynomial equations. In control rats, curves were obtained before (●) and 30 minutes after (○) onset of a hypertensive stimulus caused by aortic constriction. In acutely treated rats, curves were obtained before treatment (●), 15 minutes after treatment (△), and 30 minutes after onset of hypertension (○). Values are expressed as mean±SEM. Sla, slope before onset of hypertension; Sib, slope 30 minutes after onset of hypertension. *P<.05 compared with Sla within group.

Fig 2. Plots show pressure-nerve activity curves expressed as percentage of maximal activity vs mean arterial pressure using regression curve obtained from coefficients of third-order polynomial equations. Curves were obtained before (●) and 30 minutes after (○) onset of a hypertensive stimulus caused by aortic constriction. Values are expressed as mean±SEM. Sla, slope before onset of hypertension; Sib, slope 30 minutes after onset of hypertension.

Partial (49% to 56%) threshold shift similar to that observed in untreated rats in the present study (52%) and also in the study by Moreira et al. In chronic ACE inhibition or blockade of the Ang II receptors allowed a complete (87% to 96%) rightward curve shift to the hypertensive levels associated with a complete (88% to 94%) resetting of the systolic pressure threshold for baroreceptor activation (Fig 2). This indicates that endogenous Ang II plays an important role in baroreceptor modulation. Moreover, the similarity of results obtained with ACE inhibition and DuP 753 supports the conclusion that Ang II is involved in baroreceptor modulation and that the effect of ACE inhibition is related to blockade of Ang II formation. In addition, the fact that the bradykinin antagonist Hoe 140 did not change the effect of enalapril precludes a significant role for potentiation of endogenous bradyki-
nin in the effect of ACE inhibition on baroreceptor resetting.

The nature of the protocols used in the present study did not permit us to identify a mechanism to explain the total rapid resetting to hypertensive levels after chronic ACE inhibition or blockade of Ang II receptors. Vasopressor peptides may affect baroreceptor function acting indirectly, changing vessel wall mechanics, or they may act directly on baroreceptor neurons. There is evidence that Ang II and other peptides act indirectly, changing vessel wall mechanics, or they may act directly on baroreceptor neurons. Therefore, a more efficient relaxation ("creep") of the viscoelastic elements of the aortic wall, favoring a complete, rapid (30-minute) resetting of the baroreceptors to hypertensive levels. Nevertheless, other mechanisms, such as ionic and endothelial, could also be involved.

Rapid resetting of arterial baroreceptors has important implications for circulatory control in both physiologic and pathologic states such as arterial hypertension. The advantage of rapid resetting during hypertension is that the prevailing pressure (new pressure set point) tends to remain on the steep part of the new pressure-activity curve. This mechanism makes the baroreceptors able to discharge with a higher sensitivity to acute changes in arterial pressure around the new set point (see Chapleau et al). The arterial baroreceptor reflex regulation of heart rate in chronic hypertension is reset and blunted, ie, it shows a decreased sensitivity, whereas the reflex control of arterial pressure is only reset, ie, it does not involve an overall reduction in sensitivity. An augmentation of baroreceptor reflex function after chronic ACE inhibition has been observed in hypertensive patients as well as in spontaneously hypertensive rats. Accordingly, the increase in baroreceptor reflex sensitivity seen during chronic ACE inhibition may account for the lack of reflex tachycardia as well as for normal plasma norepinephrine and epinephrine concentrations in hypertensive subjects submitted to effective hypotensive doses of ACE inhibitors. However, it is not yet firmly established whether the primary site of action where ACE inhibitors improve baroreceptor function is at the afferent (baroreceptor activity) or central level. Even though it has been postulated that the effect of ACE inhibitors on baroreceptor reflex might be due to blockade of Ang II formation within the central nervous system due to penetration of the ACE inhibitors through the circumventricular organs, the findings obtained in the present study—of complete rapid resetting of the baroreceptors to hypertensive levels associated with unchanged baroreceptor sensitivity after chronic (7-day) ACE inhibition or blockade of AT receptors—indicate that the baroreceptor endings inside the vessel wall are a possible site of action of the ACE inhibitors on arterial baroreceptor reflex.

In conclusion, we have demonstrated that acute ACE inhibition and blockade of Ang II receptors elicited a slight fall in MAP associated with a significant increase in baroreceptor sensitivity and partial rapid resetting to hypotensive levels. In acutely treated animals, a prompt and sustained hypertensive stimulus caused by aortic constriction induced a partial rapid resetting to hypertensive levels without change in baroreceptor sensitivity. In addition, we also demonstrated that chronic (7-day) blockade of the effect of Ang II allowed a complete rapid resetting to hypertensive levels in response to a hypertensive stimulus.

Acknowledgments

Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenadoria de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). The authors acknowledge the excellent technical assistance of Jaci A. Castania and Mauro de Oliveira.

References


Chronic converting enzyme inhibition facilitates baroreceptor resetting to hypertensive levels.
V J da Silva, S V da Silva, M C Salgado and H C Salgado

Hypertension. 1994;23:I68
doi: 10.1161/01.HYP.23.1_Suppl.I68
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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/23/1_Suppl/I68