Antihypertensive Drugs Distinctly Modulate the Rapid Resetting of the Baroreceptors

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We investigated the distinct ability of various antihypertensive drugs to modulate the extent (%) of rapid (15 minutes) resetting of the baroreceptors of normotensive rats to hypertensive levels. In one protocol, hemorrhage produced a complete resetting to hypotension in rats chronically treated (6 days) with captopril. Also, hemorrhage produced only partial resetting in rats acutely treated (10–15 minutes before baroreceptor recording) with captopril and in control (untreated) rats (73±7% and 49±5%, respectively). In another protocol, all vasodilators produced hypotension in normotensive rats. Nifedipine produced complete (93±4%) resetting to hypotension, whereas prazosin produced near-maximal (83±3%) resetting. The remaining drugs studied (phenoxybenzamine, trimethaphan, and MgSO₄) induced a partial resetting (63±7%, 63±9%, and 50±5%, respectively) that did not differ significantly from the extent observed with hemorrhage in control (untreated) rats. These results demonstrate that different antihypertensive drugs distinctly modulate rapid baroreceptor resetting to hypotensive levels and that nifedipine and long-term treatment with captopril associated with hemorrhage modulate rapid resetting to hypotension in a more efficient manner. (Hypertension 1990;15(suppl I):I-63–I-67)

Data from different laboratories concerning the extent of rapid or acute baroreceptor resetting to hypotensive levels are not uniform. Dissimilarities in the extent of rapid resetting after changes in conditioning pressure might involve differences in species, methodological approaches, or both. When we investigated the effect of sodium nitroprusside, verapamil, and hemorrhage on the extent of rapid resetting to hypotensive levels in normotensive rats, we found that sodium nitroprusside modulated the phenomenon in a more efficient manner, eliciting total (complete) resetting 15 minutes after maintained hypotension.

In the present study, we quantified the ability of other antihypertensive drugs (captopril, nifedipine, trimethaphan, prazosin, phenoxybenzamine, and MgSO₄) to modulate rapid resetting. Because captopril alone does not lower mean carotid pressure to levels comparable with those obtained with the other drugs but must be accompanied by hemorrhage for such levels to be reached, we were able to investigate rats treated with captopril acutely as well as chronically.

Methods

The experiments were performed on anesthetized (sodium thiopental, 50 mg/kg i.p., Abbott Laboratories, São Paulo, Brazil) normotensive male Wistar rats weighing 250–300 g. The procedure for recording the whole-nerve activity of the aortic baroreceptor under anesthesia was the same as that used in previous studies. Carotid pressure (pressure transducer model P23Gb, Statham Instrs., Hato Rey, Puerto Rico) was recorded simultaneously with the aortic nerve discharges (differential amplifier, model 113, Princeton Applied Research, Princeton, New Jersey) on an oscilloscope (model 5113, Tektronix, Beaverton, Oregon), and the signals were stored on tape (model 3969 A, Hewlett-Packard, Palo Alto, California) for further analysis. In all experiments, the carotid pressure was monitored continuously with a thermal recorder (model 7754 A, Hewlett-Packard, Palo Alto, California).

To assess baroreceptor activity, the rats were submitted to rapid changes in arterial pressure by withdrawal and reinfusion of blood into the femoral artery. The index used to evaluate the extent of rapid resetting to hypotension was the ([ΔSPth/ΔCDP]×100) ratio, where ΔSPth represents changes in systolic threshold pressure for baroreceptor activation and ΔCDP represents changes in
carotid diastolic pressure.\(^4\) This ratio is similar to that used by Munch et al\(^5\) except we used carotid diastolic pressure instead of mean carotid pressure. After control measurements, the rats were submitted to hemorrhage (protocol 1) or received an infusion or bolus injection of one of the antihypertensive drugs into the femoral vein (protocol 2). Hemorrhage or the amount of each drug used was selected to produce a fall in mean carotid pressure (MCP) of approximately 35% of the control value. The hypotensive level was strictly maintained by controlled hemorrhage or intravenous infusion of the drug. The results for the rats treated with bolus injection (phenoxybenzamine or prazosin) refer to those rats with hypotensive levels that did not change over a period of 15 minutes.

**Protocol 1: Captopril Plus Hemorrhage**

Normotensive rats were submitted to chronic (6 days, 30 mg/kg/day p.o.) or acute (10–15 minutes before recording baroreceptor activity, 10 mg/kg i.v. bolus) treatment with captopril. After anesthesia and before recording the control baroreceptor activity, the rats were submitted to intravenous injection of angiotensin I (Ang I) (100 ng/kg i.v. bolus) to determine the effectiveness of converting enzyme inhibition. The lack of a hypotensive response to Ang I was used as an index of converting enzyme inhibition. A third group of rats (control) was not submitted to any previous treatment with captopril. After control recording of baroreceptor activity, all groups were submitted to maintained controlled hemorrhage for 15 minutes followed by measurement of baroreceptor firing range.

**Protocol 2: Hypotensive Effects of Antihypertensive Drugs**

All of the antihypertensive drugs studied (trimethaphan, phenoxybenzamine, prazosin, MgSO\(_4\), and nifedipine) produced, by themselves, conspicuous hypotension in normotensive rats. After recording the control (pretreatment) baroreceptor activity levels, all groups were maintained in hypotension for 15 minutes, and the baroreceptor firing range was recorded again. The drugs were diluted in saline and administered at the following doses: trimethaphan, 2 mg/kg/min; nifedipine, 50 mg/kg/min; MgSO\(_4\), 40 mg/kg/min; phenoxybenzamine, 3 mg/kg bolus; and prazosin, 1 mg/kg bolus. Drug dosage was adjusted to be given in a volume of 0.1 ml as bolus or infused at a rate of about 0.1 ml/min.

The results are presented as mean±SEM. The paired \(t\) test was used to determine whether the extent of resetting within each group was partial or total (complete or maximal). The unpaired \(t\) test and one-way analysis of variance (\(F\) test) were used for comparisons among groups. Changes were considered significant at \(p<0.05\).

**Results**

The effect of hemorrhage on baroreceptor firing range in control rats and rats chronically or acutely treated with captopril are presented in Figure 1. The fall (%) in MCP and the corresponding extent of rapid baroreceptor resetting after maintained (15 minutes) hypotension are presented in the inset in the lower right corner. The rats treated chronically or acutely with captopril presented a slightly but significantly lower MCP (113±2 and 114±3 mm Hg, respectively) as compared with the control rats (123±3 mm Hg). Hemorrhage elicited a downward shift of the baroreceptor firing range in all three groups, but only the chronically treated rats presented a complete (91±8%) resetting of the baroreceptors as shown by the absence of a significant difference between the SPth (73±2 mm Hg) and the CDP (65±2 mm Hg). In the acutely treated rats, hemorrhage promoted an extent of resetting (73±7%) not significantly different from that observed in chronically treated rats, but because of the significant difference between the SPth (80±3 mm Hg) and the CDP (71±3 mm Hg) of the rats, the observed extent of resetting was considered to be only partial. Hemorrhage alone promoted the smallest extent of resetting (49±5%) in control rats even though it decreased MCP more effectively (40±3%).

The hypotensive effect of different vasodilators (trimethaphan, phenoxybenzamine, MgSO\(_4\), prazosin, and nifedipine) on baroreceptor firing range are presented in Figure 2. The inset in the lower right corner shows the fall (%) in MCP and the corresponding extent of resetting. The rats treated with trimethaphan, phenoxybenzamine, MgSO\(_4\), prazosin, and nifedipine did not show a significant difference in MCP during pretreatment (109±2, 111±2, 105±3, 107±3, and 116±6 mm Hg, respectively), whereas the rats treated with MgSO\(_4\) exhibited a significantly smaller MCP during pretreatment (105±3 mm Hg) than the rats treated with nifedipine (116±6 mm Hg). Even though the maintained hypotension produced by all treatments elicited a downward shift of the baroreceptor firing range, only nifedipine produced a complete (93±4%) rapid resetting, as shown by the absence of a significant difference between the SPth (74±2 mm Hg) and the CDP (74±2 mm Hg) of the rats. Treatment with prazosin promoted an extent (83±3%) of rapid resetting not significantly different from the treatment with nifedipine, but due to the significant difference between the SPth (61±3 mm Hg) and the CDP (53±2 mm Hg) of the rats, this extent of resetting is still considered partial. Furthermore, phenoxybenzamine, trimethaphan, or MgSO\(_4\) produced changes in MCP similar to hypotensive levels that were associated with a partial extent of rapid resetting (inset, Figure 2).

**Discussion**

In the present study, we investigated the distinct ability of some antihypertensive drugs to modulate...
the extent of rapid (15 minutes) resetting of the aortic baroreceptors after maintained hypotension. In the first protocol, hemorrhage produced a downward shift of the baroreceptor firing range to hypotensive levels in chronically or acutely captopril-treated rats significantly greater than in control (untreated) rats. Whereas long-term treatment with captopril promoted a complete (91±8%) rapid resetting, the acute treatment promoted near-maximal (73±7%) resetting. Although there is no reasonable explanation for this difference, except for the duration of treatment (angiotensin converting enzyme was inhibited in both groups), these data demonstrate the ability of captopril to modulate the rapid resetting to hypotension. To our knowledge, the effect of captopril on baroreceptor activity has not yet been investigated. In conscious, sodium-depleted dogs, captopril elicited a resetting of the whole baroreceptor reflex, and it was suggested that, besides having a central effect, the converting enzyme inhibitor might be acting peripherally at the receptor level.⁶ Captopril can affect baroreceptor activity directly by an intrinsic effect, by reducing the circulatory levels of angiotensin II, or by both. It was previously demonstrated in experiments with single fibers that angiotensin II increases the firing rate of the carotid sinus nerve of the cat, but the response is abolished by reserpine.⁹

In the second protocol, all antihypertensive drugs studied elicited hypotension by themselves, with no need for combination with hemorrhage. Nifedipine was the only drug that showed a total (93±4%) rapid resetting; prazosin produced near-maximal (83±3%) resetting, and the remaining drugs (phenoxybenzamine, trimethaphan, and MgSO₄) induced only partial resetting. The results obtained with these last compounds did not differ significantly from the effect of hemorrhage on the extent of resetting of control (untreated) rats. Although the fall in MCP elicited by nifedipine was significantly smaller than that observed with MgSO₄ and prazosin, the overall percent changes in MCP were within a relatively narrow range (31±5% to 40±2%) that presumably did not interfere significantly with the extent of rapid resetting.

The calcium antagonist nifedipine induced an extent of resetting (93±4%) markedly different from that (39±2%) previously observed in our laboratory⁴ for verapamil. Our data, however, do not support the observation made in a study on the carotid sinus nerve of dogs¹ that nifedipine and verapamil have opposite effects on baroreceptors,
arch preparation raised the threshold pressure for baroreceptor activation and reduced baroreceptor sensitivity pointed to a role of Mg$^{2+}$ in modulating baroreceptor function. The similar effect of MgSO$_4$ and hemorrhage in control rats indicates that, although Mg$^{2+}$ can act physiologically to control and regulate Ca$^{2+}$ entry into smooth muscle cell,$^{14}$ it is not more efficient in affecting the degree of rapid resetting than a change in conditioning pressure elicited by hemorrhage only. Trimethaphan presented a slight but not significantly greater extent of rapid resetting (63±9%) than hemorrhage in control rats. The ganglion blockade did not facilitate the rapid resetting even considering that trimethaphan has some direct effect on the smooth muscle of the vessels.$^{15}$

The overall results support the notion that different vasodilators can modulate rapid baroreceptor resetting in different ways. Only nifedipine and long-term treatment with captopril associated with hemorrhage were able to completely reset the baroreceptors to hypotensive levels, as observed

unless species' difference or methodological approaches are taken into account. Prazosin induced a near-maximal (88±3%) rapid resetting of the baroreceptors. Prazosin has also been studied with respect to the whole baroreceptor reflex. Harron et al.$^{10}$ have suggested that the $\alpha_1$-agonist, methoxamine, decreases the sensitivity of the baroreceptor reflex, whereas other investigators$^{11,12}$ have proposed that changes in baroreceptor reflex sensitivity can be caused by an intrinsic effect of prazosin on the baroreceptors. The extent of resetting elicited by prazosin was significantly smaller than that observed with phenoxybenzamine. The fact that prazosin is more specific for $\alpha_1$-adrenergic receptors does not help explain the difference in rapid resetting observed after sympathetic blockade.

Hypotension produced by MgSO$_4$ elicited an extent of rapid resetting (50±5%) similar to that caused by hemorrhage in control rats, but significantly different from the extent observed with nifedipine. Previous observations$^{13}$ that increased extracellular concentration of Mg$^{2+}$ in the aortic
previously with sodium nitroprusside. Furthermore, prazosin and acute treatment with captopril associated with hemorrhage induced a near-maximal rapid resetting. On the other hand, the antihypertensive drugs (captopril, nifedipine, and prazosin) that presented the greatest degree of rapid resetting have different mechanisms of action that make it difficult to understand their effect on the mechanisms of rapid resetting. They share with sodium nitroprusside, however, an arteriolar and venous vasodilator effect that might be relevant for the interpretation of their modulatory action.

The distinct ability of antihypertensive drugs to modulate rapid resetting emphasizes the difficulty in comparing the extent of rapid resetting when different approaches (e.g., hemorrhage alone, hemorrhage plus drugs, or drugs alone) are used to change the conditioning pressure for driving the resetting.

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References

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