DuP 753 Is More Effective Than Captopril on Baroreceptor Function in High-Renin Hypertension

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Abstract
High-renin hypertensive rats exhibit a general impairment of the baroreceptor reflexes. In the present study we compared the effect of the angiotensin converting enzyme inhibitor captopril (10 mg/kg per day) with the effect of the selective angiotensin subtype 1 receptor blocker DuP 753 (10 mg/kg per day) on the baroreceptor reflex bradycardia (progressive doses of phenylephrine) and baroreceptor reflex tachycardia (progressive doses of nitroprusside) in conscious rats 7 days after aortic ligation. Arterial pressure was markedly reduced after both acute (15-minute) treatment with captopril (123±6 versus 184±23 mm Hg) and DuP 753 (140±10.5 versus 181±5.4 mm Hg), but the depressed baroreceptor reflex bradycardia increased only after DuP 753 (1.13±0.19 versus 0.38±0.12 bpm/mm Hg). Neither DuP 753 nor captopril administered acutely (15 minutes) or for 2 days significantly altered the depressed baroreceptor reflex tachycardia. We conclude (1) that DuP 753 was more efficient than captopril in the reversal of the depressed baroreceptor reflex sensitivity for bradycardic responses of rats with high-renin hypertension even when the reversal of hypertension was similar, and (2) that within the first 2 days, neither DuP 753 nor captopril significantly reverted the depressed baroreceptor reflex tachycardia. (Hypertension. 1994;23[suppl 1]:I-64-I-67.)

Key Words • pressoreceptors • renin • bradycardia • tachycardia • captopril • losartan

Methods
Male Wistar rats weighing 300 g were used. One day before the experiment, an indwelling catheter was implanted into the femoral artery and exteriorized through the back of the animal for measurement of blood pressure. Blood pressure was determined in conscious, freely moving rats with a strain-gauge transducer (P23Db, Statham, Hato Rey, Puerto Rico) connected to a recorder (7754A, Hewlett-Packard, San Diego, Calif). Rats were housed individually in small metal cages.
during the recording session. Heart rate was measured by means of arterial pressure pulses.

Aortic ligation between the renal arteries was performed with rats under ether anesthesia 7 days before the experiments. This experimental model of hypertension is characterized by high levels of plasma renin activity, as demonstrated in our previous study. Accordingly, we found in nine hypertensive rats of the present experiment plasma renin activity values of 23.8±5.2 ng angiotensin I/mL per hour versus 2.6±0.7 in six control rats. Baroreceptor reflex bradycardia was produced by increasing doses of phenylephrine (0.25 to 8.0 µg) injected into the femoral vein and reflex tachycardia by the injection of increasing doses of sodium nitroprusside (0.25 to 8.0 µg/mL) in the same vessel in conscious, unrestrained rats. Five groups of rats were studied: In group 1 (n=7), 10 mg/kg IV DuP 753 was injected after the control baroreceptor reflex sensitivity test, and the test was repeated after 15 minutes. Group 2 rats (n=9) were similar to group 1 except that the drop in mean arterial pressure produced by DuP 753 was corrected by phenylephrine infusion (3 to 17 µg/min). Group 3 rats (n=7) were similar to group 1 except that 10 mg/kg IV captopril was administered instead of DuP 753. In group 4 rats (n=9), the baroreceptor reflex sensitivity test was repeated after 2 days of DuP 753 (10 mg/kg per day IV) administration. In group 5 rats (n=7), the baroreceptor reflex sensitivity test was repeated after 2 days of captopril (10 mg/kg per day IV) administration. Baroreceptor reflex sensitivity was expressed as the mean ratio of all changes in heart rate to all changes of mean arterial pressure (at least three pressure increases or decreases of 10 to 30 mm Hg were used to calculate baroreceptor reflex sensitivity). Results are expressed as mean±SEM; the Wilcoxon test was used to analyze the effects of DuP 753 and captopril administration on reflex bradycardia and tachycardia. The Kruskal-Wallis test was used to analyze the differences between the treatments (ie, DuP 753 versus, captopril). Statistical significance was accepted at a value of P<0.05.

Results

Acute Effect

Arterial pressure was markedly reduced after a 15-minute injection of both captopril (123±6 versus 184±23 mm Hg) and DuP 753 (140±10 versus 181±5.4 mm Hg). Heart rate was not significantly altered (Fig 1). Although the depressed baroreceptor reflex bradycardia significantly reversed after DuP 753 (1.13±0.22 versus 0.75±0.60 beats per minute [bpm]/mm Hg), it remained attenuated after captopril (0.54±0.086 versus 0.30±0.076 bpm/mm Hg). When the drop in arterial pressure produced by DuP 753 was corrected by phenylephrine infusion, the increase in the depressed bradycardia was no longer observed (Fig 1). Neither DuP 753 nor captopril administered acutely significantly altered the depressed baroreceptor reflex tachycardia.

Chronic Effect

After 2 days of treatment (Fig 1), captopril decreased arterial pressure (95±5 versus 184±23 mm Hg) more than DuP 753 (119±6 versus 172±4.6 mm Hg). In contrast, the depressed baroreceptor reflex bradycardia remained unchanged after captopril treatment (0.46±0.13 versus 0.31±0.076 bpm/mm Hg) and reversed with DuP 753 (1.13±0.19 versus 0.38±0.12 bpm/mm Hg). In contrast, neither DuP 753 nor captopril administered for 2 days significantly altered the depressed baroreceptor reflex tachycardia (Fig 2).

Discussion

The major finding of the present study is that only DuP 753 increased the depressed baroreceptor reflex bradycardia in a high-renin model of hypertension in rats, even though DuP 753 and captopril were equally effective in reducing the increased mean arterial pressure. Moreover, neither DuP 753 nor captopril administration significantly altered the depressed tachycardia. In contrast, reversal of baroreceptor reflex bradycardia but not tachycardia has been described after acute captopril administration in other models of hypertension. The impairment of the baroreceptor reflexes associated with chronic RAS overactivity seems to be of central origin and specific for the baroreceptor reflex, because we have shown previously that the reflex bradycardia produced by ether inhalation, which is triggered by different neurogenic pathways, remained unchanged. In contrast, baroreceptor reflex bradycardia was impaired in rats with high-renin hypertension. Accordingly, the peripheral part of the vagus nerve was unaltered because the heart rate responses to electrical stimulation of the vagus nerve were also normal in rats with renal hypertension 12 days after aortic ligation.
which again suggested a central origin of the abnormality.

In the present study DuP 753 reverted the depressed baroreceptor reflex bradycardia in high-renin hypertensive rats. This effect could be attributed to a decrease of blood pressure per se as we have demonstrated previously and/or to a direct effect of DuP 753, the central depressing effect of heart rate in the baroreceptor reflex pathways. Indeed, we provided evidence that both the indirect and direct effects are important because captopril into the central nervous system may explain why DuP 753 was more effective in the reversal of the depressed baroreceptor reflex bradycardic responses. Bradykinin injected into the solitarii-vagal complex of conscious rats potentiated the baroreceptor reflex bradycardia, whereas a long-acting potent bradykinin antagonist (Hoe 140) decreased the responses, indicating that bradykinin may exert a physiological role on the nucleus tractus solitarius modulating the baroreceptor reflex bradycardia. In this way, captopril, as an angiotensin converting enzyme inhibitor increasing the kinins locally, should be more effective than DuP 753 on the depressed baroreceptor reflex bradycardia. However, the major difference should be attributed to the fact that DuP 753 has been shown to cross the blood-brain barrier in vivo and to block the angiotensin subtype 1 receptor in different brain nuclei, including the nucleus tractus solitarius and dorsal motor nucleus of the vagus nerve, whereas the gain access to brain structures inside the blood-brain barrier by captopril is not so effective.11

Regarding the fact that DuP 753 only affected reflex bradycardia and not reflex tachycardia, it should be mentioned that acute Ang II administration caused selective impairment to loading (bradycardia) but not to unloading (tachycardia) of the baroreceptor.12 Finally, it was demonstrated that central chronic captopril administration reversed the decrease in baroreceptor reflex sensitivity in spontaneously hypertensive rats,13 and intracerebroventricular infusion of enalapril augments the baroreceptor reflex responses to phenylephrine but not to sodium nitroprusside.14

In summary, the data of the present study suggest that, not only when the Ang II effect is initiated (acute administration) but also when the effect is suppressed (DuP 753), baroreceptor reflex bradycardia is more rapidly affected than baroreceptor reflex tachycardia.

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References


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