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±0.22 versus 0.75±0.60 beats per minute [bpm]/mm Hg) and remained attenuated after captopril (0.54±0.086 versus 0.30±0.07 bpm/mm Hg). After a 2-day treatment, captopril reduced arterial pressure (95±5 versus 184±2.3 mm Hg) to lower levels than DuP 753 (119±6 versus 172±4.6 mm Hg), whereas the depressed baroreceptor reflex bradycardia remained unchanged with captopril (0.46±0.13 versus 0.31±0.076 bpm/mm Hg) and increased with 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 I):I-64-I-67.)

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

Acute administration of angiotensin II (Ang II) in rabbits inhibits the decrease in lumbar sympathetic activity but not the increase in discharges observed during hypotension. Moreover, only reflex bradycardia is inhibited, leaving reflex tachycardia unaltered.1 It seems that the acute administration of Ang II effectively blocks the inhibition exerted by the baroreceptors on the sympathetic outflow, thus exaggerating the pressor response but leaving the reflex increase in sympathetic activity elicited by hypotension relatively unaltered. Similarly, Ang II antagonists injected directly into the nucleus tractus solitarius selectively enhance reflex bradycardia but not reflex tachycardia.2 Nitroprusside-induced tachycardia also is not altered by saralasin or Ang II microinjection into the nucleus tractus solitarius in conscious rats.3

On the other hand, different results have been obtained when baroreceptor reflex was studied in chronic high-renin renal hypertension. For instance, in rabbits with renal hypertension an abnormality of the baroreceptor reflex control of sympathetic outflow, as well as impairment of reflex bradycardia and reflex tachycardia have been observed. These abnormalities are related to the duration of the hypertension.4 Previously, we observed a marked inhibition of both reflex bradycardia and reflex tachycardia in rats with mild or severe hypertension induced by aortic ligation.5 Normalization of renin-angiotensin system (RAS) activity in rats with mild hypertension coincided with normalization of the bradycardic responses, whereas the alteration persisted in those rats with severe hypertension in which hyperactivity of the RAS also persisted. More recently we observed that high-renin renal hypertensive rats not only had impaired reflex control of heart rate during increases and decreases in arterial pressure but also their reflex responses of renal sympathetic nerve activity to loading and unloading of the baroreceptors were attenuated.6 Thus, chronic overactivity of the RAS in high-renin hypertension produced a general impairment of the baroreceptor reflex control of the circulation. The present experiment was designed to study whether the reversal of RAS overactivity by administration of captopril or the selective angiotensin subtype 1 antagonist receptor DuP 753 (losartan) would also revert the abnormality of baroreceptor function present in rats with high-renin hypertension of 7 days.

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 ng/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 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 ± 0.07 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 ± 23.3 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, which produced a marked recovery of hypertension (normalization), could be due to the partial recovery of the baroreceptor gain sensitivity in group 1 but not in group 2, whereas the blockade of Ang II was similar in both groups.

Different degrees of penetration of DuP 753 and 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.

Regarding the fact that DuP 753 only affected reflex bradycardia and not reflex tachycardia, it should be mentioned that acute Ang II administration caused reflex bradycardia and not reflex tachycardia, it should be remembered that acute Ang II administration caused reflex bradycardia and not reflex tachycardia, it should be remembered that acute Ang II administration caused reflex bradycardia and not reflex tachycardia, it should be remembered that acute Ang II administration caused reflex bradycardia and not reflex tachycardia.

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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