Effect of Angiotensin-Converting Enzyme Inhibitor Quadropril on Dynamic Parameters of Vascular Tone under Conditions of NO Synthesis Blockade in Normotensive and Spontaneously Hypertensive Rats

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The role of NO in the mechanism of quadropril modulation of the flow-dependent vasodilation was examined in normotensive (Wistar) and spontaneously hypertensive (SHR) rats. The abdominal aorta was cannulated and autoperfused at different volume rates to obtain the pressure–flow curves. In the first experimental series, the blood flow–pressure dependence was measured before and after intravenous injection of quadropril (1 mg/kg). In the next series, this dependence was obtained before and after injection of NO-synthase inhibitor L-NNA (10 mg/kg) and quadropril, respectively. Quadropril potentiated vasodilation caused by an increase in perfusion volume rate in both normo- and hypertensive rats and stabilized intravascular pressure. Inhibition of NO synthesis elevated hydraulic resistance and decreased stability of intravascular pressure in normo- and hypertensive rats. In normotensive rats, these changes were promoted by a decrease in vascular distensibility. Under these conditions, quadropril pronouncedly potentiated the flow-dependent vasodilation only in SHR rats, which was revealed methodically by an increase in perfusion rate in the posterior quarter of the body. Thus, in SHR rats the quadropril-potentiated vasodilation in response to increased perfusion rate does not depend on NO synthesis.

Key Words: *nitric oxide; quadropril; spontaneously hypertensive rats*

Potentiation of flow-dependent vasodilation in normotensive animals by inhibitors of angiotensin-converting enzyme (ACE) was reported in many papers [2,4,7]. However, the peculiarities of the effects of ACE inhibitors in hypertensive animals are still to be clarified. Endothelial dysfunctions, specifically disturbances in NO synthesis/bioavailability, are typical of arterial hypertension [5,6] and can result in attenuation of the endothelium-dependent effect of ACE inhibitors. In this respect, the question arises on the role of NO in flow-dependent vascular dilatatory response under the effect of ACE inhibitors in hypertensive animals.

Our aim was to examine the effects of ACE inhibitor quadropril on steady-state and dynamic parameters of the vascular tone. In addition, we examined the relation of the quadropril modulation of the flow-dependent vasodilation to its effect on NO secretion in normo- and hypertensive rats.

MATERIALS AND METHODS

The study was carried out on male normotensive Wistar rats (n=14) and male spontaneously hypertensive rats (SHR, n=13). The animals were initially narco-

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tized with intraperitoneal Nembutal (5 mg/100 g) followed by intravenous basal narcosis with α-chloralose (60 mg/kg). Artificial ventilation was performed via tracheostome at respiratory volume 3 ml/100 g body weight and respiration rate 50 min^{-1} under the action of myorelaxant dithylinum (suxamethonium chloride, 0.2 mg/kg every 15-20 min). A segment of the abdominal aorta was isolated below the renal arteries and used for controlled perfusion of the posterior quarter of the body. The cannulated proximal and distal ends of the aorta were connected to the input and output of the pump, respectively. Short-term (0.5-1.0 min) stepwise changes in the volume flow rate were performed in such a way that the new steady-state levels of perfusion pressure fell into the range of 50-250 mm Hg. The measured flow-pressure data were used to calculate the changes in hydraulic resistance R_{hyd}, vascular distensibility (VD), and intravascular pressure stability (IVPS) before and after injection of the test drug. VD was assessed by changes of hydraulic resistance in response to elevation of perfusion rate. IVPS was calculated as the inverse value to the difference between the maximum and minimum perfusion pressure values within the range of variations in the perfusion rate, which was the same before and after injections of the drug. The flow-dependent vasodilation was assessed on the basis of VD index [1]. After obtaining control samples, quadropril (1 mg/kg) or N^G-nitro-L-arginine (L-NNA, a blocker of NO synthase, 10 mg/kg) were injected intravenously and the measurements were repeated after 20-25 min. Under the action of L-NNA, the range of perfusion rate narrowed to 2-5 ml/min. In both groups of rats, perfusion pressure rose to maximum physiological values ~250 mm Hg with increasing perfusion rate to 5±1 ml/min. Therefore, the vascular tone indices were assessed by analyzing blood flow–pressure curves in the range of perfusion rate from 2 to 5 ml/min. After making measurements against the background of L-NNA treatment, the rats were intravenously injected with quadropril (1 mg/kg) and the measurements were repeated after 20-25 min.

Changes in the examined indices during the experiments were compared using nonparametric tests. The data were presented as the mean and standard deviation. Significance of differences between the indices measured before and after injection of the drugs was assessed with paired Wilcoxon *T*-test at $p<0.05$. The difference between two independent samples were evaluated using the Wilcoxon–Mann–Whitney *U*-test. The data were processed using Statistica software.

RESULTS

In Wistar rats, the initial BP and HR were 111±18 mm Hg and 416±35 bpm, respectively. In SHR, the corresponding values were 166±32 mm Hg (significantly higher than in Wistar rats) and 384±18 bpm. In 20-25 min after intravenous injection of quadropril (1 mg/kg), BP decreased by 19.3±7.0% and by 17.7±5.7% ($p<0.05$, Wilcoxon test) in normotensive and SHR rats, respectively. At the same time, HR did not significantly change in both groups.

In Wistar rats, quadropril significantly decreased maximum R_{hyd} corresponding to maximum perfusion rate ($p<0.05$, Fig. 1) and slightly decreased minimum R_{hyd} value. These effects were accompanied by elevation of VD and IVPS. In SHR, quadropril also decreased maximum R_{hyd} ($p<0.05$) without significant changes in the minimal R_{hyd}. Similarly, it elevated VD and IVPS indices.

For evaluation of the role of NO in quadropril-induced vascular effects, this drug was injected intravenously at the same dose in addition to previously injected L-NNA. After inhibition of NO synthesis (before quadropril injection), BP values were 139±10 mm Hg and 203±22 mm Hg in Wistar rats and SHR, respectively. The corresponding HR values were 333±29 and 330.6±20 bpm. In 20-25 min after intravenous injection of quadropril, BP decreased by 21.5±17.3% in Wistar rats ($p<0.05$, Wilcoxon test) and by 10.1±9.3% in SHR ($p<0.05$). At the same time, quadropril insignificantly increased HR to 365±18 and 360.6±23 bpm in Wistar rats and in SHR, respectively. These observations corroborate the data on moderating the hypotensive effects of ACE inhibitors in SHR by preliminary inhibition of NO synthesis [3] and attest to an important role of NO in the mechanisms of their hypotensive action in SHR.

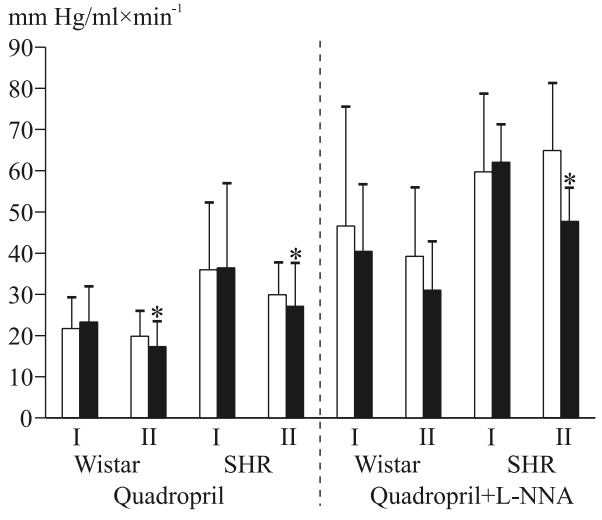

Fig. 1. Effect of quadropril (1 mg/kg) on hydraulic resistance (R_{hyd}) of arterial vessels in normotensive (Wistar) and hypertensive (SHR) rats. Ordinate: R_{hyd} at minimum (*I*) and maximum (II) perfusion rates. Here and in Figs. 2 and 3: open bars: initial values; dark bars: postinjection values. *$p<0.05$ compared to initial values.

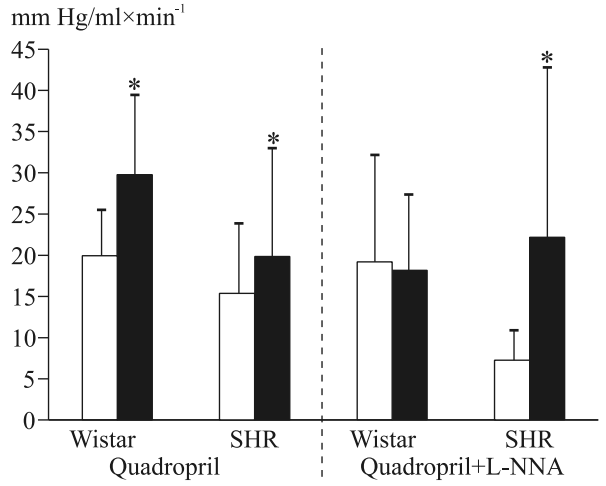

Fig. 2. Effect of quadropril (1 mg/kg) on IVPS in normotensive (Wistar) and hypertensive (SHR) rats.

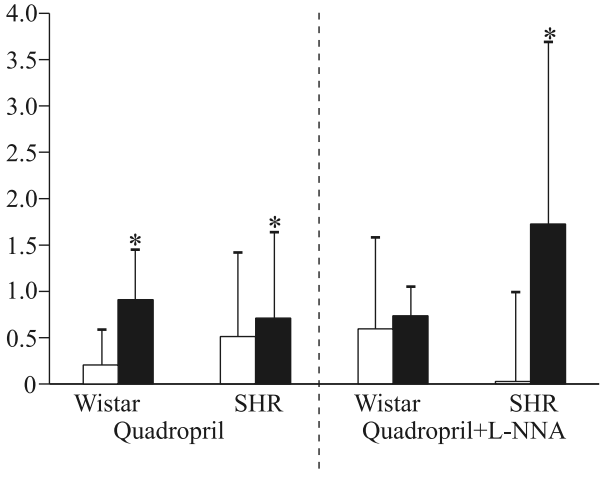

Fig. 3. Effect of quadropril (1 mg/kg) on VD (dimensionless parameter) in normotensive (Wistar) and hypertensive (SHR) rats.

SHR demonstrated higher values of R_{hyd} after injection of L-NNA both at minimum and maximum perfusion rates.

In Wistar rats, the hypotensive effect of quadropril was accompanied by insignificant decrease in R_{hyd} at minimum perfusion rate and by reduced increment in R_{hyd} in response to the increase in perfusion rate. In this group, quadropril did not significantly change VD and IVPS indices (Figs. 2 and 3).

In SHR (but not Wistar rats), quadropril increased VD in all experiments despite inhibition of NO synthesis, which attested to enhancement of flow-dependent vasodilation. Thus, elevation of perfusion rate in quadropril-treated SHR with inhibited NO synthesis up-regulated secretion of the vasodilation factors. It is noteworthy that R_{hyd} at the maximum perfusion rate was smaller than the initial value (Fig. 1). In comparison with the initial data, the changes in the perfusion rate induced smaller variations in perfusion pressure, which was reflected by elevation of IVPS.

Evidently, in contrast to normotensive (Wistar) rats, the endothelium of quadropril-treated SHR can compensate for blockade of NO synthesis by up-regulating synthesis of another vasodilator. Most probably, the agent responsible for this up-regulation is the endothelial hyperpolarizing factor [5].

Our findings suggest that the observed potentiation of flow-dependent vasodilation by quadropril in Wistar rats in the absence of NO synthesis blockade was NO-dependent. In contrast, quadropril potentiated flow-dependent vasodilation in SHR under conditions of NO synthesis blockade, which manifested in elevation of VD and IVPS. Therefore, during NO-deficiency in SHR, quadropril up-regulates synthesis of alternative relaxing factor.

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