Effect of Enalapril Treatment during Experimental Renal Deficiency in Spontaneously Hypertensive Rats

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A subtotal nephrectomy is traditionally used for studying the nonimmune mechanisms of the development of nephrosclerosis [3] and for testing the methods of correction of chronic renal deficiency (CRD) in experiment [8]. It has been shown that treating normotensive Wistar rats subjected to resection of no less than 5/6 of the renal tissue, resulting in a decreased number of functionally active nephrons, with inhibitors of the angiotensin 1-converting enzyme (ACE) has a preventive effect on the development of structural changes in the glomeruli due to a decrease of the excess intraglomerular pressure (IGP) [6]. We performed comparative assays of the course of experimental CRD in rats of different genetic lines which revealed that spontaneously hypertensive rats (SHR) with some specific features of systemic hemodynamics [2], of calcium metabolism, and of vasculary wall permeability for protein [1] exhibit a reliably faster development of nephrosclerosis and azotemia than normotensive Wistar rats [1]. In a view of this, the aim of the present investigation was to study the efficiency of ACE inhibitors (enalapril) during experimental CRD in SHR.

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MATERIALS AND METHODS

Male SHR weighing 200 g (six control and six experimental animals) were used to create a model of CRD. Surgical removal of 2/3 of the tissue of one kidney was performed under ether anesthesia. The contralateral kidney was removed a week later. Immediately after the second operation the animals received drinking water containing enalapril (Renitec, MSD) in a dose of 75 mg/liter.

Before the first stage of the operation and then weekly 24-h urine was collected in a metabolic chamber under conditions of water deprivation. Blood samples were taken from the caudal vein and examined during the first stage of the operation and then weekly. The concentration of urea (UC) and of creatinine was measured in the urine and blood. Twenty four-hour proteinuria (PU) and the rate of glomerular filtration (RGF) according to the clearance of endogenous creatinine were determined. Before the first stage of the operation and just before sacrifice the arterial pressure (AP) was measured in the caudal artery.

The control animals were subjected to the same operation, but were not treated with enalapril. All animals were kept on a high protein diet (no less than 40% protein) and given water ad libitum. The animals were killed 1.5 months after the second stage of the operation. The remaining kidney was fixed with formalin and then embedded in

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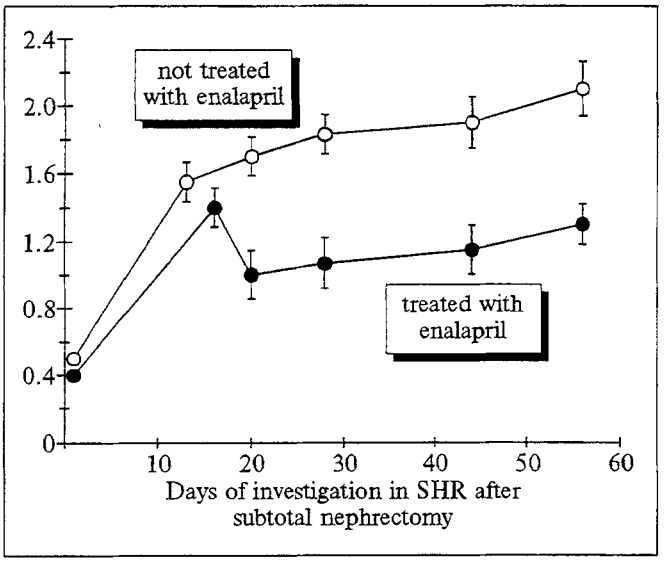

Fig. 1. Dynamics of UC indexes (ordinate, mM) in the serum.

paraffin; the slides were stained with hematoxylin-eosin, chromotrope, and PAS. Data of the histological assay were assessed in points (from 0 to 3) depending on the magnitude of the changes in the glomeruli, tubules, and interstitium.

The data were statistically processed using the Student t test. Differences in the magnitude of the structural alterations were also estimated by the nonparametric Wilcoxon-Mann-Whitney U test.

RESULTS

There was a reliable elevation of the serum UC 15 days after the operation (Fig. 1) in all experimental rats. However, while this index continned to rise in the control group, reaching toward the end of the experiment 23.1±1.7 mM/liter, in the rats treated with enalapril a stable level of UC was obtained during the entire succeeding period. The same phenomenon was observed for the dynamics of PU and RGF (Figs. 2 and 3). The indexes of AP of the control rats (172.0±8.4 mm Hg) did not differ from the AP level in the rats treated with enalapril (182.0±11.2 mm Hg).

The morphological study revealed no pronounced changes of the interstitium except in the zone adjacent to the postoperative scar. The glomeruli were hypertrophic in all animals, but especially so in the control rats. Inosculation of the capillary loops, proliferation of the mesangium cells, matrix expansion, and deposition of fibrin in the capillaries were more pronounced in rats not treated with enalapril. In the proximal tubules there was granular degeneration, as attested to by the reversible intensity of the processes of protein reabsorption, and hyaline degeneration, testifying to a depletion of this reabsorption. Moreover, destruction of the brush border and hypertrophy of the tubule epithelium were observed. All these features were reliably more expressed in the control rats. Dystrophy and cystic dilatation were observed more often (but not reliably) in the control.

Thus, enalapril administration in SHR exhibiting at the time of the operation an increased permeability of the arteriole wall for protein, associated with relatively low AP [1], had a preventive effect on the development of structural and functional changes in the kidney, just as in normotensive rats [7].

It is well known that the main pathogenic factor in the development of kidney sclerosis induced by circulatory insufficiency is an elevation of the IGP [6], resulting in damage to the en-

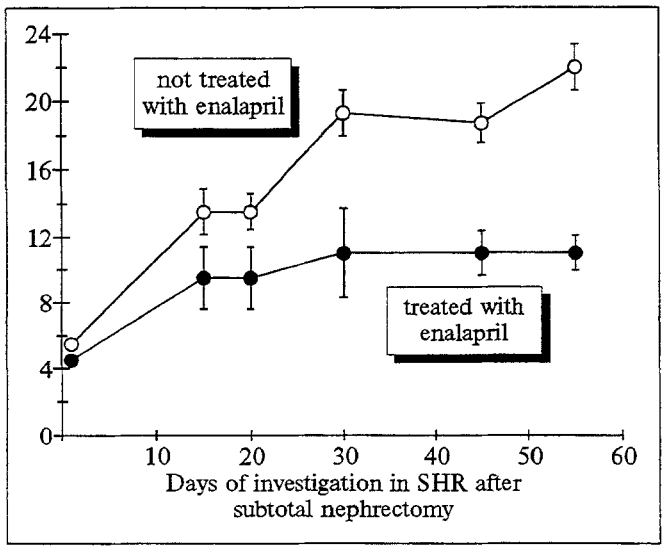

Fig. 2. Dynamics of PU indexes (ordinate, g/liter).

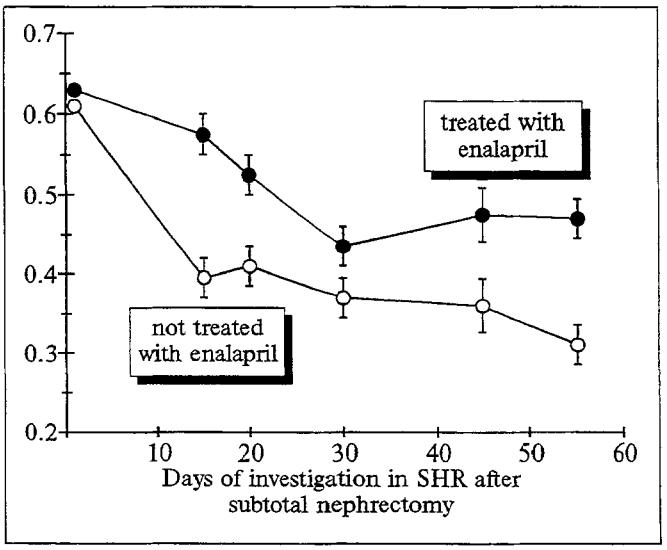

Fig. 3. Dynamics of RGD (ordinate, ml/min).

dothelium and initiating a cascade of pathological reactions leading to glomerulosclerosis [8]. A morphological criterion of damage to the endothelium is the appearance of fibrin in the lumen of the glomerular capillaries [9]. Analysis of the structural changes revealed a reliably more frequent deposition of fibrin in the glomerular capillaries in the control rats. Moreover, the rats treated with enalapril demonstrated a less pronounced PU (Fig. 2) and a slower decrease of filtration (Fig. 3), i.e., the indexes rapidly reacting to circulatory failure and change of IGP were less affected [8]. These facts permit us to conclude that this drug is effective in IGP regulation not only in normotensive rats, but also in animals with an initially damaged permeability of the vascular wall for protein [1].

It is especially to be noted that a therapeutic effect of the drug was obtained under conditions of a protein-enriched diet, and therefore enalapril may be thought to abolish the negative effects of the protein load in CRD. The mechanism of action of the protein load is complex and has not been clarified. However, it is known that the protein load enhances glomerular filtration [5] due to stimulation of the bradykinin-kinin system and, in addition, it provides for enhancement of eikosanoid synthesis, in particular, of thromboxane [4]. By blocking the effect of the protein load on thromboxane synthesis [4], enalapril preserves the endothelium from the damaging action of the latter.

The absence of a pronounced hypotensive effect of the drug in our experiment calls for further investigation. It probably attests to a predominant effect of ACE inhibitors on the level of thr individual glomerule, holding out promise for on the use of this drug for the retardation of CRD progress in the absence of severe systemic hypertension.

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