Acta Veterinaria (Beograd), Vol. 46. No. 1, 3–16, 1996.

UDK 619:615.225.2

THE EFFECTS OF ANTIHYPERTENSIVE DRUGS ON THE KIDNEY VASCULAR COMPLICATIONS OF HYPERTENSION IN THE SPONTANEOUSLY HYPERTENSIVE RAT

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(Received, 21. November 1995.)

The aim of this study was to examine the effects of antihypertensive drugs on the kidney blood vessels in spontaneously hypertensive rats. Three antihypertensive drugs with different mechanisms of action were used: the beta adrenergic blocker-propranolol, the vasodilatator-hydralazine and an inhibitor of the angiotensin I converting enzyme-captopril. They were given to the rats in tap water every day, during 5 weeks. Every week during the experiment, arterial blood pressure was measured by an indirect method and heart rate was calcilated for each animal (including the control group). Finally, the rats were sacrificed and pieces of kidney were taken for pathohystological and morphometric analysis of interlobular arteries. After 5 weeks of treatment, the results wereas follows in all three experimental groups, arterial blood pressure was decreased comparing to the control group; there was no correlation between the level of blood pressure and the degree of damage to the blood vessels. The drug which decreased arterial pressure the most was hydralazine, but it did not affect the degree of damage to kidney blood vessels. Captopril was very effective both in decreasing the blood pressure and lowering the degree of damage to kidney blood vessels, while propranolol did not have a great effect either on the arterial blood pressure of on vascular changes in kidneys. The results showed that arterial blood pressure was not the only factor in the genesis of vascular complications, became other factors, like the renin-angiotensin system, also have an importent role in that process (the results showed that captopril had the greatest protective effect concerning damage to the blood vessels, but it did not have the greatest effect in decreasing of arterial blood pressure).

Key words: kidney, hypertension, captopril, hydralazine, propranolol

INTRODUCTION

Chronic hypertension is followed by many complications in different organ systems, which consequently provoke diseases of the arterial part of the vascular bed. We could define two categories of vascular changes. One group would be "funnctional" changes, or, called by Folkow, "structural" changes (Folkow et all., 1958; Folkow et al., 1973) where muscular hypertrophy ocours in the walls of

arterial veseels. The other group of damage would be pathoanatomic changes (microangiopathies) where there is fibrinoid necrosis, musculo-mucoid hyperplasy of the intima and hyalin arteriolosclerosis. During hypertension, many arteriosclerotic changes are apparant on the kidney blood vessels which increases the negative effects of the main disease and produces damage to the kidney tissue. In investigations of the etiology and pathogenesis of arterial hypertension, the best experimental models are rats with genetically caused hypertension (Smirk and Hall, 1958), e. g. spontaneously hypertensive rat (SHR) strains (Okamoto and Aoki, 1963; Okamoto at al., 1972; Yamori, 1982). The significant thickness of the walls of blood vessels in SHR forms an ideal investigation model for antihypertensive therapy.

The aim of this study was to examine the effects of antihypertensive drugs, which decrease arterial blood pressure by different mechanisms, upon the degree of pathologic changes in the kidney vascular bed in SHR using propranolol (beta blocker), captopril (blocker converting enzyme) and hydralazine (vasodilator).

MATERIAL AND METHODS

Male SHR, 3 months old, and weighing approximately 300 g were used in this experiment. The rats were the 14 th generation descendents of breeders originally obtained from Taconic Farms, Germantown, NY. All rats were given standard rat chow (Veterinarski Zavod, Zemun) and tap water ad libitum. They were randomly divided into 4 groups of 11 rats each. During the experiment 2 animals died (one from the control group, and one from the captopril group), so those groups had 10 animals each.

Group 1 (K), control, untreated CHR

Group 2 (P), SHR given propranolol (a beta adrenergic inhibitor), dissolved in the drinking water (2 g/L). Calculated on the basis of daily water intake, the average propranolol dose was 120 mg/kg/day

Group 3 (C), rats given captopril (angiotensin I converting enzyme inhibitor) dissolved in the drinking water (1g/L). The average daily captopril intake was 60 mg/kg.

Group 4 (H), SHR given hydralazine (a vasodilatator) dissolved in drinking water (100 mg/L), so that the average daily dose was 6 mg/kg.

Body weight, arterial blood pressure and heart rate were determined every fourth day three times before the begining of the experiment, and once a week, during the experiment. At the end of the experiment, which lasted for 5 weeks, the animals were sacrificed under pentobarbital anesthesia (Nembutal, 35 mg/kg b. w.) by exsanguination. After this, the kidneys were taken for hystological analysis.

Methodology

1. Indirect method of measuring blood pressure: Blood pressure was registered in the tail artery of unanesthetised rats by a modification (Lozzio at al., 1972) of the method of Maistrello and Matscher (1969), using a tail cuff. First the

rats were placed under an IR lamp for 10-15 minutes. Registration of the blood pressure was performed in a special cage, where the bottom was heated by an electric heater up to 40 degrees C. The tail was put into the tail cuff of 20 mm length, which was inside a metal cylinder. A pneumatic pulse detector, which was connected to a transducer, was fixed to the tail distally from the tail cuff. The method of measurement was sphygmomanometric. The air was pumped inside the tail cuff above the level of the arterial pressure. As the pressure in the tail cuff slowly decreased we were registreing pulse. The moment pulse oscillations showed was the level of the systolic pressure. For easier calculation, the decrease of pressure in the tail cuff and the pulse were registered on the same channel of a writing recorder (Physiograph Four, Narco Bio Systems, Inc.). For a more precise estimation of pressure, we took the average number of three measurements.

We agree with the opinion, that we can obtain exact results when: 1. the length of the tail cuff is 18-20 mm (Maestrello annd Matscher, 1969) annd 2. the instrument for detection of pulse oscillations is sensitive enough (Pfeffer et al., 1971; Bunag, 1973).

2. Histological procedure: Parts of the kidney were always taken in the same way. After the kidneys had been removed from the body, the kidney's poles were removed by sharp knives. Each kidney was cut transversally in the middle. We put one piece of kidney which was 2-3 mm in size in 10% formalin fixative.

After that the kidney tissue was treated by a standard hystological procedure. The thickness of the sections were 2-3 microns. We used the following staining techniques:

He (haematoxylin-eosin) for general analysis of tissue, PAS (Periodic Acid Achiff), method for showing mucopolysacharides, *Silver impregnation* for reticular fibres, *Massonn trichrom* for collagen and *Silver methenamin* for glomerular basal membrane.

The stained kidney sections were examined under an "Orthoplan" microscope and photographs taken using kodak-Chrome film.

3. Morphometric method: Photographs of size 6x9 cm were analysed by the morphometric method using professional morphometric equipment (Leitz-Wetzlar) with:

1. a PC for morphometric research - model "Leitz-ASM 68 K"
2. the software packet "SORBAS" based on its own operative system "SUSY"
3. a printer "SIEMENS PT 88 ink-jet"

Five photographs were taken of each experimental and control group.

We traced characteristic blood vessels of the kidney from the photographs to tracing paper using a drawing table with Kulmann aparatus size A3. We measured:

- the external radius
- the thickness of the wall
- and the luminal radius

For each characteristic blood vessel. Each parameter was measured 6 times for each blood vessel, in order to obtain enough variables for adequate statistical analysis. The random choice problem of specific measurement place of adequate parametar was solved. The model of 6 planes was made and put over the measured object, always in the same position. Measured parameters were entered in the computer automatically by using graphic table and "light pencil" which were parts of the described computer with a special purpose.

Statistical analyses were done according to Steel annd Torrie (1960). Bonferroni's modification (Wallenstein at al., 1980) of Student's t test for multi-group comparison was used to test the significance of differences among the groups. The results were expressed as means + 1SEM.

RESULTS

In figure 1, blood pressure in the tail artery during the 5 week experiment is shown for all 4 groups of animals. At the beginning of the experiment, there was no statistical difference between the groups. However, durinng the first week we observed a significant decrease of blood pressure in the groups receiving captopril and hydralazine and in second week only in the group treated captopril

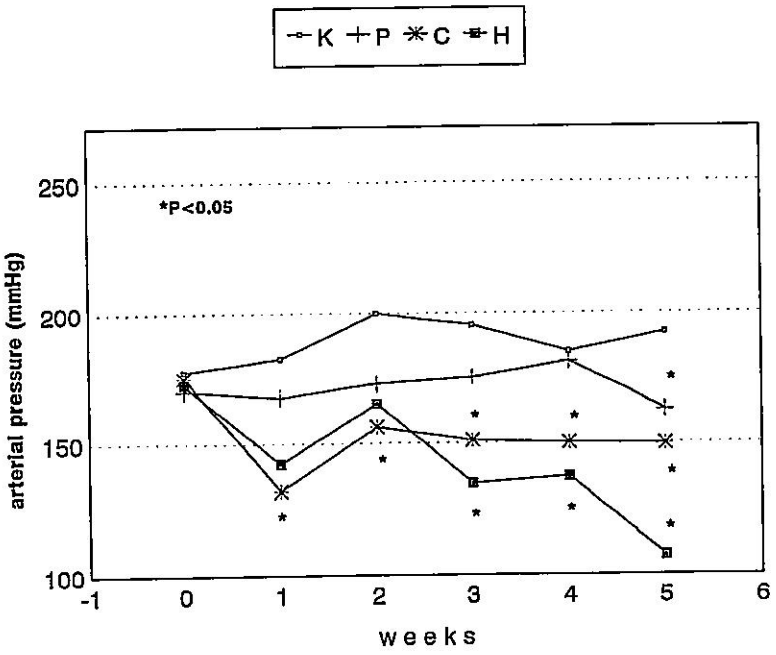


Figure 1. Changes of arterial pressure during 5 weeks

(p>0.05). The decrease of blood pressure was significant in the groups treated with captopril and hydralazine in the third and fourth week, and at the end of the experiment there was a significant decrease in all three treated groups (captopril, propranolol, hydralazine), compared with the controls (p<0.05).

Concerning heart beat frequency, at the beginning there was no significant difference between the groups. During the experiment a significant decrease of heart frequency occurred in the group treated with propranolol, comparing with the control group (p<0.05) except in the second week. The other groups did not show significant differences comparing with the control group during 5 weeks of treatment (Figure 2).

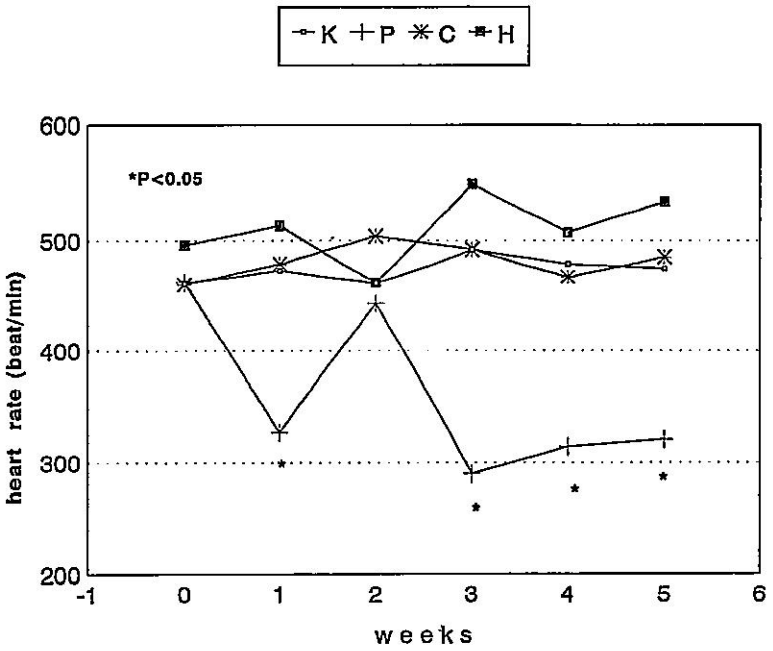


Figure 2. Changes of heart rate during 5 weeks

Thickened walls of the interlobular arteries with emphasized muscular cells, and narrow lumen could be observed for the kidnneys of all groups. (Figure 3).

The internal elastic lamina was prominent (Figure 4).

Animals which were treated with propranolol had thickened walls all along the interlobular arteries (Figure 5).

The lumen was narrow but not so emphasized. The internal elastic lamina was very undulated, with preserved continuity (Figure 6).

Figure 3. Arteria interlobularis with thickened wall, emphasized muscular cells and narrow lumen
Control, H & E, 10 x 25

Figure 4. Emphasized internal elastic lamina of the blood vessel
Control, Paff Halmi, 10 x 25 x 2

Figure 5. Thickened wall of interlobular artery with narrow lumen but not so emphasized
Propranolol, Masson trichrom, 10 x 25.

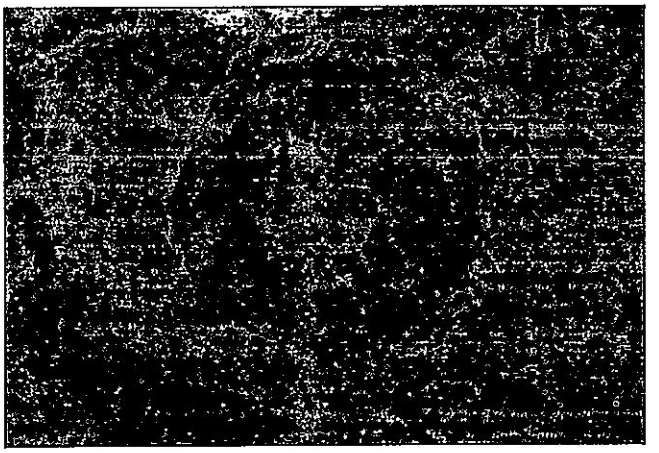


Figure 6. Internal elastic lamina is very undulated, preserved continuity
Propranolol, Paff Halmi, 10 x 25

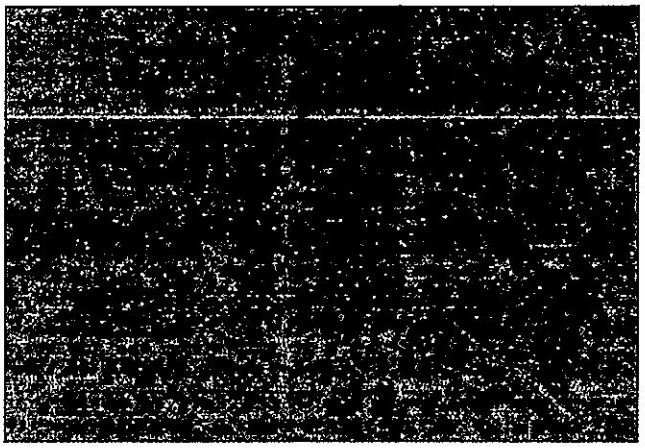
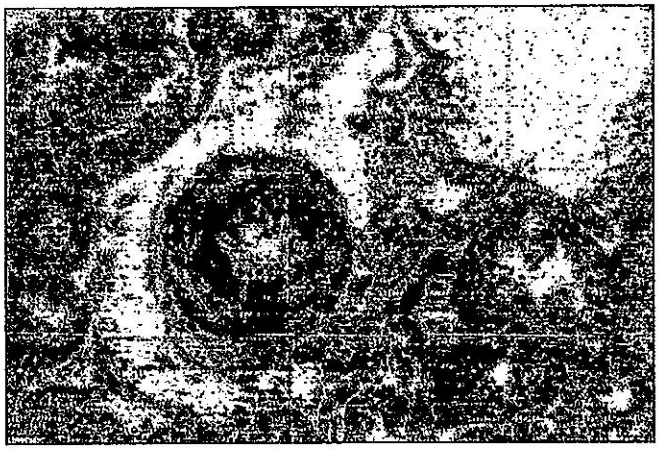


Figure 7. The blood vessels are very thickened with narrow lumens which are, from place to place, like a narrow crack
Hydralazine, PAS, 10 x 25 x 2



The internal elastic laminna in all animals from this group is very undulated and thickened
Figure 8. Hydralazine, Paff Halmi, 10x25 2

The blood vessels in the animals treated with hydralazine, had very thickened walls and narrow lumens which were, from place to place, like a narrow crack (Figure 7).

The internal elastic lamina in all the animals from this group was very undulated and thickened (Figure 8).

Figure 9. Artery wall is thinner annd lumen is wider
Captopril, Masson trichrom, 10x25.

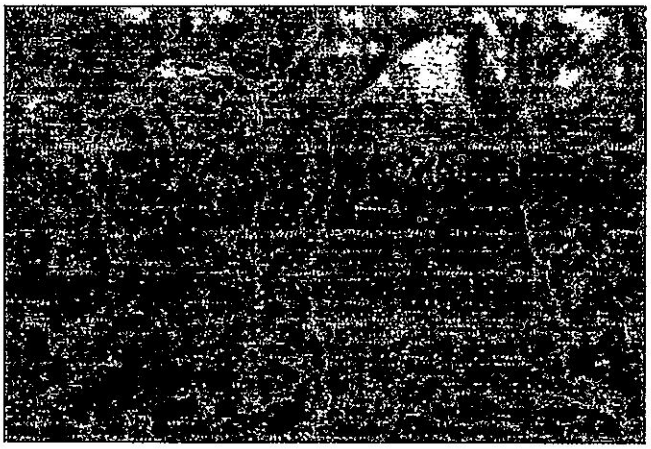


Figure 10. Internal elastic lamina is thiner and is less undulated
Captopril, Paff Halmi, 10 x 25

In the group of animals treated with captopril the artery wall was thiner and the lumen was wider (Figure 9).

This was confirmed by morphometric analysis (Table 1).

Moreover, the internal elastic lamina was thinner and less undulated (Figure 10).

The results of morphometric analyses, the thickness of the wall, the whole radius of the blood vessel and the luminal radius for all four groups, showed that the lumen of the blood vessels of animals treated with captopril was significantly wider ($p<0.05$) compared with the controls, while the lumen of blood vessels of animals treated with hydralazine did not show any significant difference compared to the controls (Table 1).

Table 1.

Animal group	Lumen diameter μm	Wall thickness μm	Blood vessel diameter – μm
Control (K)	32.73 ± 4.694	45.73 ± 3.893	111.8 ± 23.22
Captopril (C)	52.85 ± 10.79	27.00 ± 3.897	107.9 ± 22.02
Hydralazine (H)	16.91 ± 3.382	28.05 ± 3.401	83.12 ± 16.97
Propranolol (P)	61.39 ± 15.35	56.44 ± 7.55	176. ± 44.16

The ratio of the luminal radius and the thickness of the wall of interlobular arteries, was significantly higher in the group of rats treated with captopril compared to the other groups (Figure 11).

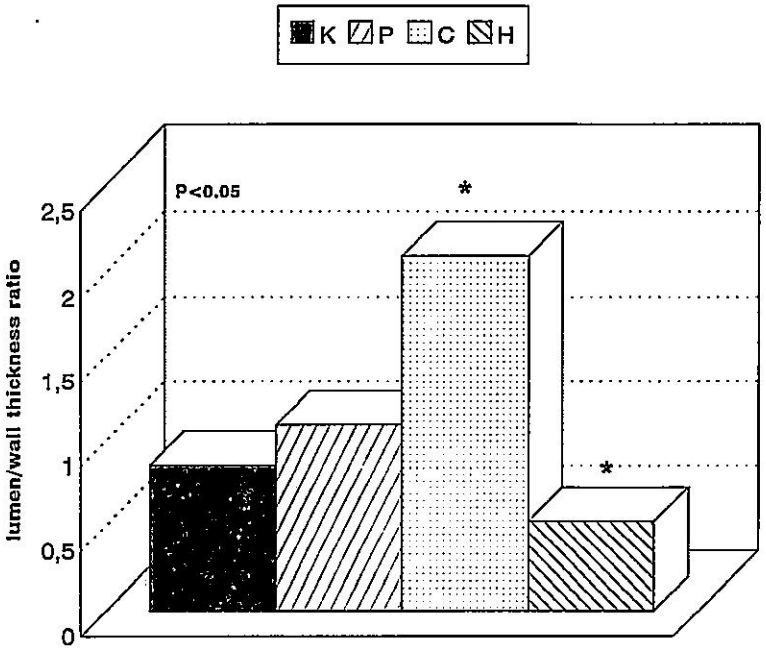


Figure 11. Relationship between the lumen of the blood vessel and wall thickness

In the group of animals treated with hydralazine, that ratio was significantly lower (Figure 11).

DISCUSSION

The results presented in this study showed that in spontaneously hypertensive rats there were changes in kidney blood vessels characteristic for increased arterial blood pressure. The basic change was hypertrophy of the muscle layer which was evident from the results that showed the very thick arterial walls and decreased ratio between the luminal diametar and the wall of blood vessels aa. interlobulares).

These results confirm data (Mandal et al. 1978; Johson and Murihead 1981). Pathohystological changes in the kidney blood vessels were relatively small and similar to the changes in the initial phase of hypertension (Mandal at al. 1978). We used young animals where pathohistologic changes were reversible because we wanted to see whether a decrease of arterial blood pressure could lead to alleviation of the damage to blood vessels.

Treatment with antihypertensive drugs led to a decrease in blood pressure in these rats. We used three antihypertensive drugs with different mechanisms: a blocker of beta-adrenergic receptors (propranolol), an inhibitor of angiotensin I converting ennzyme (captopril) and a direct vasodilator (hydralazine). All three drugs decreased the arterial blood pressure similarly to the results of other authors (Fagard et al. 1981; Cody et al. 1981; Gerber and Nies 1983).

Our results for all four groups of animals showed that there need be no correlation between the level of arterial blood pressure and the degree of damage to blood vessels. Thus, the group of animals treated with hydralazine, which had the lowest level of arterial blood pressure during the whole experiment, exibited a similar degree of changes in blood vessels as in the control group. The narrowing of the lumen was very marked and the ratio between the luminal radius and the thickness of the wall was significantly smaller at the group of animals which received hydralazine compared to the 3 other groups. In the group of animals treated with captopril, the lumen of the blood vessels and the ratio between luminal radius and wall thickness was much bigger than in the other experimental groups. Treatment with propranolol caused a relatively small decrease of arterial blood pressure and did not have a great influence on morphologically important parameters in SHR.

Other authors have also reported that there was no correlation between the efficency of some drugs to decrease arterial blood pressure in hypertensive animals and the prevention or alleviation of vascular complications of hypertension (Owenns 1987; Freslonn and Guidicelli 1983; Jaspersen at al. 1985; Limas at al. 1984; Dworking at al. 1988; Nordborg 1987; Smeda at al. 1988; Stacy and Prewitt 1989). Owens (1987) showed that propranolol decreases the arterial blood pressure in SHR, but does not change the degree of hypertrophy in smooth muscle cells of aortal tunica media, more than we could assume on the basis of the effect on the basis of the effect on the arterial blood pressure. This was also found in our study (Figure 11). On the other hand, captopril is of much more use

in the prevention of hypertrophy of smooth muscular cells in the aorta, but has little effect on the arterial blood pressure, which was presented in our study too (Figure 11). Similarly it was shown that captopril was much more effective than dihydralazine in the prevention of hypertrophy of the aorta in SHR in spite of their identical effect on the blood pressure (Freslon and Guidicelli, 1983). Also it was demonstrated that hydralazine caused a decrease of arterial blood pressure in SHR but did not prevent structural changes in the mesenterical arteries. As our results showed, there was no lessening of changes in the walls of Kidney interlobular arteries. On the contrary, the greatest thickness of the wall and the narrowest lumina occurred in the animals treated with hydralazine (Table 1: Figure 7,8) while the thickness of the interlobular arterys walls in animals treated with captopril was decreased (Table 1).

Based on that, Fernandes and Onesti (1976) made the hypothesis that arterial hypertension was not the only factor in the hypertrophy of the left ventricle and hypertrophy of arterial media.

Furthermore, other factors, such as: increase of activity of the renin - angiotensin system, and the sympathetic nervous system, might have a more important role. Since hypertrophy of the walls of the blood vessels and cardiac hypertrophy were present in the early phases in SHR, genetic factors are important in the development of both heart and blood vessel hypertrophy (Yamori et al. 1979). It may be possible to predict the development of hypertension, using this type of information, especialy concerning the early development of cardiac hypertrophy. That would be applicative by conntrolling arterial blood pressure in the childhood and echocardiograph research of heart volume (Yamori et al. 1979). Cardiac hypertrophy that could be seen by determinantion of heart dimensions could be used to detect a genetic predisposition for early hypertension in humans. It is important to mention that the effect of antihypertensive drugs on vascular changes, especially on hypertrophy of smooth muscular cells, could be absent because od the trophic influence provoked by icreased sympathetic activity which could be a conseguence of the increased arterial pressure caused by that drug. Decreased arterial blood pressure induced by ay drug leads to activation of baroreceptors and also to ann increase of sympathetic activity. It is known that sympathectomia leads to a decrease in the thickness of blood vessels because of decreased proliferation of smooth muscular cells (Beven 1975) and it was logical to predict that an increase of symphaticus activity would cause hypertrophy of smooth muscular cells in the blood vessels. Therefore, we might predict that a possible decrease of vascular hypertrophy, caused by returning the blood pressure to a normal state in animals treated with hydralazine, would be prevented by proliferation of smooth muscle cells because of increased sympathetic activity, following stimulation of baroreceptors. The effect of captopril on hypertrophy of smooth muscular cells, which, simultaeously with decreasing of arterial blood pressure by influencing the renin - angiotesin system, decreases the activity of symphaticus, would not be blocked. Thus, we may predict that the absence of correlationn between the level of arterial blood pressure and the degree of hypertrophy of vascular smooth muscle was actually a consequence of differences in the sympathetic nervous system which were caused by using

some antihypertensive drugs. This analysis showed that vascular changes in hypertension may be determined by the level of arterial blood pressure and that the efficiency of some drugs in stoping vascular hypertrophy depends primarily of their effects on the activity of symphaticus.

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EFEKTI ANTIHIPERTENZIVNIH LEKOVA NA BUBREŽNE VASKULARNE KOMPLIKACIJE HIPERTENZIJE KOD SPONTANO HIPERTENZIVNIH PACOVA

GORDANA RADUJKOVIĆ - KUBUROVIĆ

SADRŽAJ

U radu je ispitivan efekat antihipertenzivnih lekova na stanje krvih sudova bubrega kod spontano hipertenzivnih pacova. Korišćena su tri antihipertenzivna sredstva: propranolol (adrenergički blokator) u dozi od oko 120 mg/kg, kaptopril (blokator konverting enzima) u dozi od 60 mg/kg i hidralazin (vazodilatator) u dozi od 60 mg/kg težine tela. Pacovi su dobijali ove lekove, svakodnevno, rastvorene u vodi za piće. Eksperiment je trajao 5 nedelja. Tokom eksperimenta, svake nedelje, svim životinjama (i kontrolnoj grupi) indirektno je određivan arterijski krvni pritisak a izračunavana je frenkvenca rada srca. Po žrtvovanju, uzeto je tkivo bubrega i izvršena je patohistološka i morfometrijska analiza interlobularnih arterija. Rezultati pokazuju da, iako je u sve 3 eksperimentalne grupe arterijski pritisak, posle 5 nedelja davanja antihipertenzivnih lekova, snižen u odnosu na kontrolnu grupu, ne postoji korelacija između visine arterijskog pritiska i stepena oštećenja krvnog suda. Hidralazin najviše snižava arterijski pritisak ali praktično ne utiče na stepen vaskularnih oštećenja bubrega. Kaptopril vrlo efikasno snižava pritisak i istovremeno u znatnoj meri ublažava oštećenja krvnih sudova bubrega, dok propranolol ne utiče značajije ni na arterijski pritisak ni na vaskularne promene u bubrezima. Ovakvi rezultati ukazuju da arterijski pritisak sam po sebi nije jedini faktor u razvoju vaskularnih komplikacija hipertenzije već da i drugi činioci kao npr. sistem renin - angiotenzin (na šta ukazuje podatak da je kaptopril najefikasniji u sprečavanju vaskularnih lezija iako nije najefikasniji u snižavanju pritiska) imaju važnu ulogu.