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Does ACE inhibitor modify the morphofunctional state of the nephron?

The fact that for several years the angiotensin convertase inhibitors of high hypotensive effectiveness have been commonly used in the treatment of arterial hypertension is connected with the necessity to establish the indications and contraindications for the therapy with drugs derived from this group (10). The ACE inhibitors affect the organism with multidirectional activities (3, 5, 13, 14), among which the main link is inhibiting the transformation of the inactive form of angiotensin into angiotensin II, which is accompanied by fluctuations of the homeostasis in the organism (influence on the water and electrolyte balance). The inhibition occurs, among others, on the level of the proximal canaliculi and the regulation apparatus of the kidney. The above-described action of i-ACE may imply pathophysiologically significant morphophysiological changes of the ultra structure of cell organelle.

MATERIAL AND METHODS

Studies were carried out on white Wistar rats – males of approx. 300 g body weight. Animals were given the inhibitor of angiotensin convertase (ACE) (Captopril) in two doses: group I (10 animals) – 0.23 mg/day in two divided doses, group II (10 animals) 0.71 mg/day (also in two divided doses). The above-mentioned doses correspond to therapeutic doses of 50 mg and 150 mg/day. The medicine was administered intragastrically through a stomach tube, in the form of water suspension (1 ml). The control animals were given respectively distilled H_2O. The preparation was being applied for the period of 3 weeks. After three weeks of drug application the animals were anaesthetized in ether narcosis and specimens of the left kidney were taken up for observation in the

transmission electron microscope Tesla BS 500. The specimens of the renal cortex were embedded in Durcupan ACM Fluka resin.

RESULTS

In the kidneys of animals from experimental group I dilation of the lumen of proximal canaliculi of the nephron and the presence of scarce, microgranular deposits in the lumen were observed. In the cytoplasm of the cells there were many little vacuoles and apical vesicles. In the basal part of the cells of proximal canaliculus cytoplasm dilution was visible, as well as single vacuoles, at times, possibly related to cytoplasmic edema.

In animals from group II, vacuolization was distinctly marked in the cells of proximal canaliculi – in the basal part of the cytoplasm (Fig. 1) and sometimes there occurred a dilation of the intracellular space (Fig. 2). Many lysosomes were observed. Dilation of urinous space within the renal corpuscle was observed.

DISCUSSION

There are numerous data suggesting that convertase inhibitors may influence the hormonal function of the endothelium, increasing the release of nitrogen oxide and inhibiting the production of endothelin 1 (1). Both these substances also influence the regulation of renal hemodynamics, function of the kidneys and sodium metabolism (7).

It has been demonstrated that captopril exerts nephroprotective effect on patients with diabetic nephropathy, recording the pace of its development (2, 4). The beneficial effect of ACE inhibitor involved lowering of the intraglomerular tension of microalbuminuries and even fully symptomatic proteinuria (2, 6, 12, 14).

It was stated that during the procedure of coronary vessel bypasses a periodical attenuation of soluble substance reabsorption might occur in the proximal canaliculus, which is connected with simultaneous release of vessel-dilating mediators (nitrogen oxide, prostacyclines) (7). In rats with experimentally induced hypertension, the ACE normalizes the blood pressure, reduces proteinuria and inhibits tissue lesions (11). In the kidneys of the animals subjected to the experiment, in the cells of the proximal canaliculi dilution of the cytoplasm, numerous vacuoles in the apical and basal part of the cell, dilation of the intercellular space as well as more numerous lysosomes were observed. The above-described changes were

Fig. 1. Experimental group II. The proximal canaliculus of the kidney. Vacuoles in the basal part of the cytoplasm. Magn. 6000 x

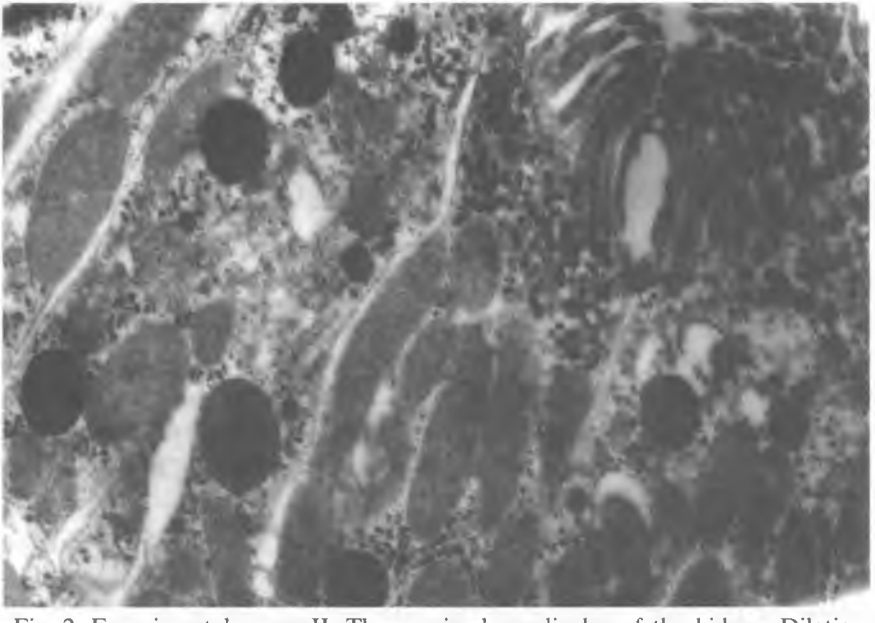

Fig. 2. Experimental group II. The proximal canaliculus of the kidney. Dilation of the intracellular space. Magn. 8000 x

more distinctly marked in animals which were given a higher dose of the drug. The studies in the electron microscope revealed morphofunctional changes of the nephron related to the application of the drug Captopril.

CONCLUSIONS

Application of Captopril may temporarily modulate the morphofunctional status of certain structures of the nephron, which was demonstrated in the foregoing experiment.

REFERENCES

1. Arcaro G. et al.: ACE inhibitors improve endothelial function in type 1 diabetic patients with normal arterial pressure and microalbuminuria. Diabetes Care, 22, 1536, 1999.
2. Chiarelli F. et al. Diabetic nephropathy in children and adolescents: a critical review with particular reference to angiotensin-converting enzyme inhibitors. Acta Paediatr., Suppl., 425, 42, 1998.
3. Filipiak K. J. et al.: Inhibitory konwertazy angiotensyny – nowe leki wieńcowe. Terapia, 2, 21, 2000.
4. Hebert L. A. et al.: Combination ACE inhibitor and angiotensin II receptor antagonist therapy in diabetic nephropathy. Am. J. Nephrol., 19, 1, 1999.
5. Kiiski R. et al.: An inhibitor of angiotensin converting enzyme (enalapril) augments endotoxin-induced hypotension in the pig. Ups. J. Med. Sci., 104, 163, 1999.
6. Van der Kleij F. G. et al.: ACE polymorphism does not determine short-term renal response to ACE inhibition in proteinuric patients. Nephrol. Dial. Transplant., 12, (Suppl. 2), 42, 1997.
7. Licker M. et al.: Chronic angiotensin converting inhibition does not influence renal hemodynamic and function during cardiac surgery. Can. J. Anaesth., 46, 626, 1999.
8. Marcisz C.: Układ renina–angiotensyna–aldosteron w stanach zaburzonej czynności tarczycy. Post. Hig. Med. Dośw., 54, 519, 2000.
9. Pawlak R., Buczko W.: Układ renina-angiotensyna a hemostaza. Kardiol. Pol., 48 (supl. II), 27, 1998.
10. Reardon L. C., Macpherson D. S.: Hyperkaliemia in outpatients using angiotensin-converting enzyme inhibitors. How much should we worry? Arch. Int. Med., 158, 26, 1998.

11. Remuzzi A. et al.: ACE inhibition induces regression of proteinuria and halts progression of renal damage in a genetic model of progressive nephropathy. Am. J. Kidney Dis., 34, 626, 1999.
12. Ruggenenti P. et al.: Renoprotective properties of ACE-inhibition in non-diabetic nephropaties with non-nephrotic proteinuria. Lancet, 354, 359, 1999.
13. Tang L. et al.: ACE inhibition and fibroblast growth factor in cultured human vascular smooth muscle. Vasc. Med., 4, 129, 1999.
14. Velasquez M. T. et al.: Role of angiotensin-converting enzyme inhibition in glucose metabolism and renal injury in diabetes. Metabolism, 47, (Suppl 1), 7, 1998.

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SUMMARY

Captopril, the inhibitor of the angiotensin convertase (ACE) was administered to white rats in two doses: 0.23 mg/day/rat and 0.71 mg/day/rat. The preparation was being applied for the period of 3 weeks. Observations were carried out in a transmission electron microscope. In the kidneys of the animals subjected to the experiment, in the cells of the proximal canaliculi dilution of the cytoplasm, numerous vacuoles in the apical and basal part of the cell, dilation of the intercellular space as well as more numerous lysosomes were observed. The above-described changes were more distinctly marked in animals which were given a higher dose of the drug. The studies in the electron microscope revealed morphofunctional changes of the nephron related to the application of the Captopril. Application of the Captopril may temporarily modulate the morphofunctional status of certain structures of the nephron, which was demonstrated in the foregoing experiment.

Czy inhibitor ACE modyfikuje stan morfofunkcjonalny nefronu?

Captopril, inhibitor konwertazy angiotensynowej (ACE), podawano szczurom białym w dwóch dawkach: 0,23 mg/dobę/szczura oraz 0,71 mg/dobę/szczura. Preparat aplikowano przez okres 3 tygodni. Obserwacje prowadzono w mikroskopie elektronowym. W nerkach zwierząt doświadczalnych obserwowano w komórkach kanalików proksymalnych rozrzedzenie cytoplazmy, liczne wakuole w apikalnej i przypodstawnej części komórki, poszerzenie przestrzeni międzykomórkowych oraz liczniejsze lizosomy. Zmiany wyraźniej zaznaczone były u zwierząt otrzymujących wyższą dawkę leku. Badania w mikroskopie elektronowym wykazały zmiany morfofunkcjonalne nefronu, związane z aplikacją preparatu Captopril. Stosowanie Captoprilu może przejściowo modulować stan morfofunkcjonalny niektórych struktur nefronu, co wykazano w niniejszym eksperymencie.