ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 119 SECTIO D 2004

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Morphological changes in adrenal cortex – the final effect of angiotensin II receptor antagonists

The glomerular layer of adrenal cortex is the source of aldosterone, the production and release of which may be directly stimulated by angiotensin (2, 3, 6, 7, 14). Angiotensin II receptor antagonists suppress the release of aldosterone, taking place under the influence of angiotensin (2, 11, 15, 16). Losartan, a highly selective antagonist of angiotensin II receptors, blocks all biological effects of angiotensin, both in the cardiovascular system and on the tissular level (3, 8, 12). The preparation turned out to be effective in the treatment of hypertension, both idiopathic and accompanying renal diseases (4).

The aim of our studies was the evaluation of the effect of various losartan doses, administered to rats, on the morphology of the glomerular layer in adrenal cortex.

MATERIAL AND METHODS

The studies were conducted on 50 (200 g) white Wistar rats from a laboratory animal breeding farm. The animals were divided into four experimental groups and one control group. The experimental animals received losartan manufactured by Adamed Ltd, containing potassium losartane as an active substance. The drug was administered for the period of four weeks, in two doses: daily human therapeutic dose (50 mg) and in a ten times larger dose. Losartan was applied in the form of a water suspension, with the use of a stomach tube, according to the rat's body mass: experimental group I - 0.14 mg/day for 4 weeks; experimental group II – the drug was administered in the same dose as in group I , then a 2-month currency period was applied, during which the rats were given, like in the control group, standard fodder and water to drink; experimental group III – losartan was administered in the dose of 1.4 mg/day for the period of 4 weeks; experimental group IV – the drug was applied like in group III, then there was a 2-month currency period.

After the experiment had finished, the rats were decapitated and their adrenals were collected for examination. The material was fixed in 4% formalin. On paraffin sections staining was carried out: survey stain H+E, tricolor stain according to the Masson's method, and staining according to the Mc Manus's method (PAS). Observations were made and photos were taken with the use of Jena Med Carl Zeiss Jena light microscope.

RESULTS

THE CONTROL GROUP

H + E staining. The glomerular layer of rat's adrenals is not a homogeneous cell stratum. It consists of small, dense glandular cells, and is separated with a stroma represented mainly by thin-walled capillaries. The cells situated near the capsule are extremely poorly differentiated locally and they constitute blastic cells of the cortex (Fig. 1). Tricolor staining, according to the Masson's method revealed the stroma of connective tissue in blue for glandular elements and sections of walls capillary vessels. Staining according to the Mc Manus's method (PAS) revealed the presence of polysaccharides in various shades of purple in the form of a delicate network of connective tissue fibres, around groups of glandular cells and the walls of blood vessels.

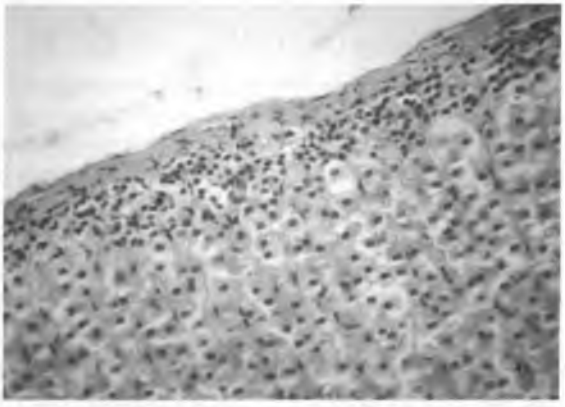

Fig. 1. Control group. Glomerular layer of adrenal cortex. H+E. Magn. 400x

EXPERIMENTAL GROUPS

I – H + E staining. On the adrenal cross-sections, the glomerular layer, like in the control group, was in the form of a heterogenic cell stratum, made of small glandular cells forming little glomes and of poorly differentiated cells laying among them, often on the whole strip. The latter cells were characterized by a dense arrangement. The intracellular borders were invisible, and the nuclei were intensely stained with hematoxylin.

II – H + E staining. Besides the clusters of glandular cells, predominating, poorly differentiated cells in a dense system were observed. The nuclei of single glandular cells were light and enlarged, with visible mitotic divisions. Single nuclei in the division stage were also observed in the cells of the fascicular layer, on the border of both layers (Fig. 2).

III – H + E staining. In the structure of glomerular layer, the dense system of cells with flattened nuclei was predominating. They often formed a wide fascicle. Below them, there were glandular cells, forming glomes.

IV – H + E staining. Like in experimental group III, the glomerular layer structure was dominated by a system of non-differentiated cells, separated by large cells, organized in glomes. The layer of poorly differentiated cells was wide and occurred also under the glomes, on the border of the fascicular layer (Fig. 3).

In the experimental groups no significant changes in the PAS reaction intensity and staining according to the Masson's method were observed as compared to the control group preparations.

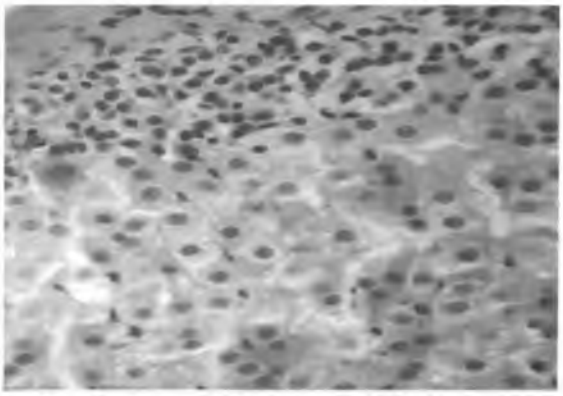

Fig. 2. Experimental group II. Glomerular and fascicular layers of adrenal cortex. H+E. Magn. ca. 800x

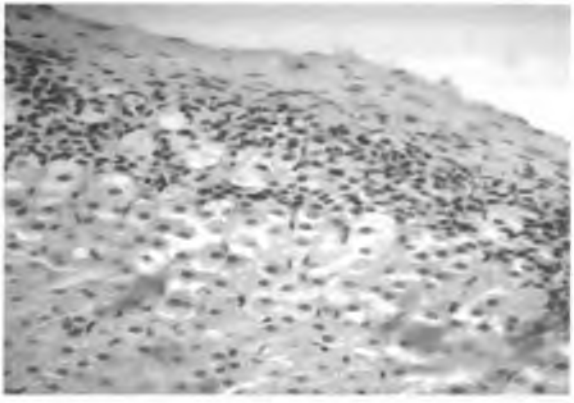

Fig. 3. Experimental group IV. Glomerular layer of adrenal cortex. H+E. Magn. ca. 400x

DISCUSSION

In the adrenals, the angiotensin II receptors (AT-1) are mainly situated in the glomerular layer (2, 5); few are present in the fascicular and reticular layers. Angiotensin, acting through AT-1 receptors, stimulates the proliferation (9, 12, 16) and hypertrophy of the glomerular layer cells (5, 9).

In the experimental conditions it was noticed that losartan inhibits the proliferative activity of angiotensin (9,12,16). In our experiment, in rats receiving losartan in the therapeutic dose for the period of 4 weeks (experimental group I), in the structure of the glomerular layer of adrenals poorly differentiated cells prevailed. Similar arrangement occurred in the adrenals after a 2-month break in the administration of the drug. This difference was most noticeable in the group of animals receiving ten times larger dose of the drug (experimental groups III and IV).

In the experimental group II (2-month break in drug administration), single divisions of the glomerular and fascicular layer cells were additionally observed, especially on the border of these two layers. Both the first and the second observation indicate that losartan, administered to rats for the period of 4 weeks in the therapeutic and ten times higher dose, impoverishes the adrenal glomerular layer in glandular cells. Thus, it probably causes the decrease of aldosterone synthesis.

After a 2-month break in losartan administration in the therapeutic dose (experimental group II), the reconstruction of glandular cells was noticed, which was proved by the observed mitotic divisions.

Besides aldosterone biosynthesis, an important activity of the glomerular layer cells is the renovation of adrenal cortex cells (10), which was observed in our experiment (a 2-month break in drug administration). After a 2-month break in drug administration in a dose ten times larger than the therapeutic one, glandular cells organized in glomes, were larger than in the previous experimental groups.

CONCLUSIONS

1. Losartan, administered to white rats in the therapeutic and ten times higher dose for the period of 4 weeks influences the histological image of the adrenal cortex.

2. The impoverishment of the glomerular layer in glandular cells after administration of the drug probably influences the amount of aldosterone released by the adrenals.

3. After a 2-month break in losartan administration, reconstruction of glandular cells is noticeable, which indicates transitory character of the observed changes.

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SUMMARY

The influence of losartan, angiotensin receptor on the histological image of the adrenal glomerular layer of white rats was revealed. The drug was administered in the therapeutic and ten times higher dose. It was manifested by the decrease of glandular cells and prevalence of blastic cells of the cortex. After a 2-month break in drug administration, the reconstruction of glandular cells was noticed, which could indicate that the observed changes are of transitory character.

Zmiany morfologiczne w korze nadnerczy efektem docelowym aktywności antagonistów receptora angiotensyny II

Wykazano wpływ losartanu – antagonisty receptora angiotensyny II, podawanego w dawce terapeutycznej i dziesięciokrotnie większej przez okres 4 tygodni, na obraz histologiczny warstwy kłębkowatej nadnerczy szczurów białych. Wyrażało się to ubytkiem komórek gruczołowych i przewagą komórek blastycznych kory. Po dwumiesięcznej przerwie w podawaniu leku zauważalna była odbudowa komórek gruczołowych, co wskazywałoby na to, że zaobserwowane zmiany mają charakter przejściowy.