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RESERVE RENIN PRODUCTION BY GLOMERULAR MESANGIAL CELLS AFTER EXPERIMENTAL REDUCTION OF THE RENAL CIRCULATION

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The abdominal aorta of rats was constricted between the orifices of the renal arteries. Renin activity was studied separately in the capillary part of the isolated glomeruli and in their arterioles. Renin activity was found in the capillary part of the glomeruli 3-4 weeks after the operation, and evidence of activation of the granular and agranular endoplasmic reticulum and Golgi complex was found in the mesangial cells. The results are interpreted as confirmation of the postulated reserve production of renin by the mesangial cells during a prolonged reduction in the renal circulation.
KEY WORDS: renin; mesangial cells; juxtaglomerular apparatus; renal hypertension; body reserves.

Many morphological investigations have shown a common origin of the juxtaglomerular (JGC) and mesangial (MC) cells and the appearance of similar changes in them in various situations. However, the physiology of MC has not yet been studied. Theoretical views of reserve powers in physiological systems [3], based on biogenetic principles and data in the literature on the morphology of MC during stimulation of the juxtaglomerular apparatus (JGA), have suggested that MC are reserve sources of renin [4].

The investigation described below was carried out to test this hypothesis.

EXPERIMENTAL METHOD

A nichrome wire loop was tied around the abdominal aorta of Wistar rats weighing 160-250 g, between the orifices of the renal arteries. The diameter of the loop was chosen so as to reduce the blood flow in the left kidney by about 75% [2]. The animals were killed at weekly intervals during the first 1.5 months of the experiment, and then 2 and 3 months after the operation. Intact rats served as the control. The blood pressure in the carotid artery of all the animals was measured before sacrifice by means of a strain gauge. Individual glomeruli and their JGA were isolated from the left kidney by the method of Dahlheim et al. [7] and the fragment containing arterioles was separated from the capillary glomerulus proper (the capillary fragment) by microdissection. Renin activity (RA) was determined in each fragment by the writers' modification of the

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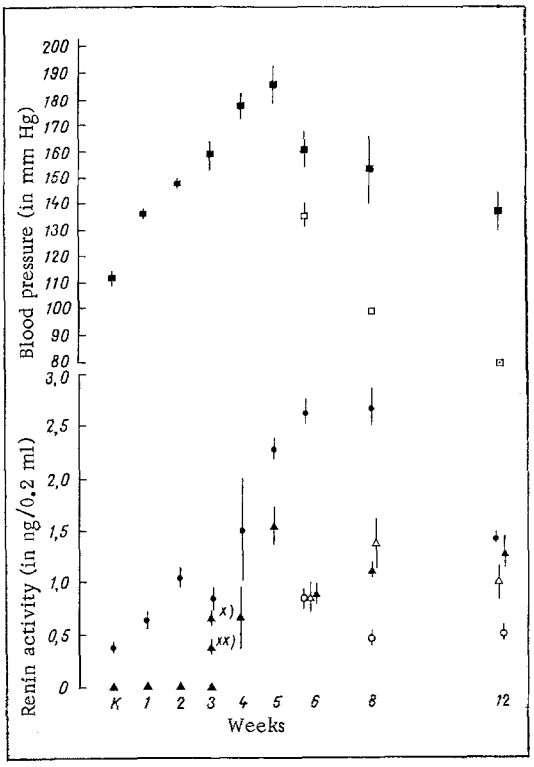

Fig. 1. Dynamics of blood pressure (squares) and RA in course of experiment in arteriolar (circles) and capillary (triangles) fragments. Filled symbols – rats of group 1; empty – rats of group 2. C) Control. ×) RA found in 100% of samples; ××) RA found in 60% of samples.

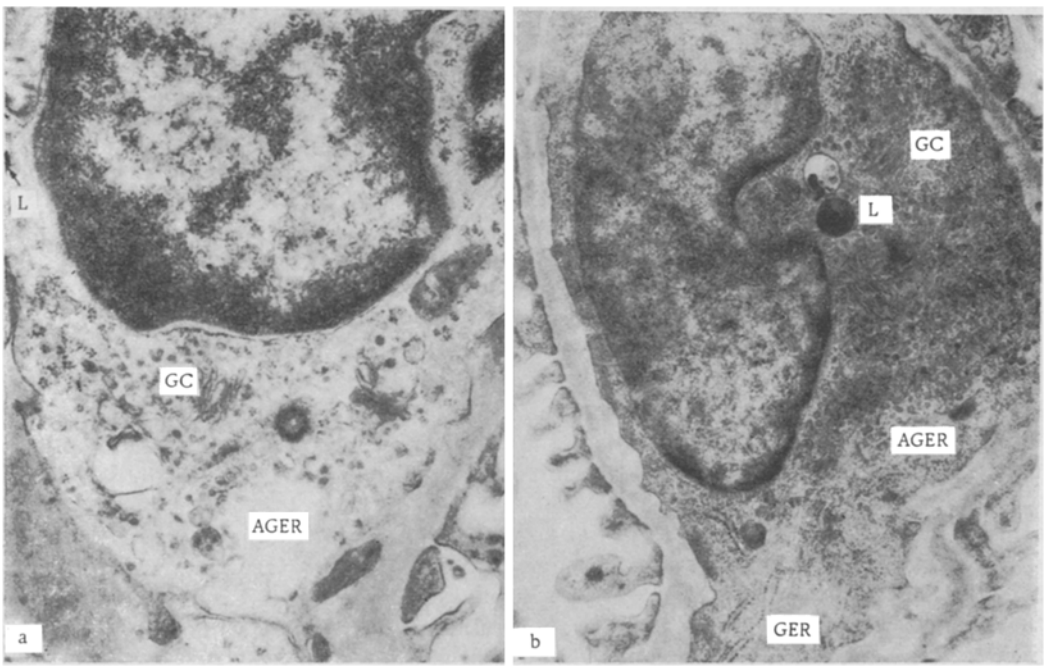

Fig. 2. Ultrastructure of MC. a) Control: weak development of organelles of synthesis and secretion (40,000 ×); b) 6 weeks of ischemia: activation of synthetic and secretory processes (36,000 ×). GER) Granular endoplasmic reticulum, AGER) agranular endoplasmic reticulum; GC) Golgi complex; L) lysosomes.

method of Dahlheim et al. [7]. To plot calibration curves standard solutions of angiotensin-2 amide (Ciba, Switzerland) were used. The results were expressed in nanograms of angiotensin formed per 0.2 ml of incubation mixture. Parallel samples of material were taken for electron-microscopic investigation.

EXPERIMENTAL RESULTS

The left kidney of the experimental animals was reduced in size and ischemic. During the last 1.5 months of the experiment it developed sclerosis, the intensity of which increased toward the end of the experiment.

Renin activity in the arteriolar fragment increased gradually so that after 5 weeks it was five times higher than the control. The animals killed at subsequent times could be divided into two groups, differing sharply in RA in this locus. In group 1 (eight rats) RA continued to rise and by the eighth week it reached values six or seven times higher than the control, after which it fell by about half. In the animals of group 2 (five rats) RA fell sharply from the sixth week and by the end of the experiment it was almost indistinguishable from the initial level (Fig. 1). The blood pressure of these animals at these times was below the control level and cortical necrosis of the kidney was observed. The number of renin granules in JGC of the experimental animals was higher than in the control throughout the investigation, but the morphology of the granules was the same as that observed in the control.

Renin activity was first found in the capillary fragment only 3 weeks after the operation: In one animal it was found in all samples tested, in another in only 60%, whereas in the other four animals killed at this time no RA was found in any of the samples. Renin activity was found in every sample of all rats after 4 weeks and later, and reached its maximum for each particular locus 5 weeks after the operation, after which it fell initially and then rose again slightly, to remain at a steady level thereafter until the end of the experiment (Fig. 1). It is noteworthy that virtually no difference was found between the groups of experimental animals with respect to this index. In MC the volume of cytoplasm was increased compared with the control and the number of profiles of the endoplasmic reticulum and Golgi complex was increased. Contents of average electron density were present in the elements of the granular reticulum and the number of ribosomes on their membranes was increased. No specific (renin) granules were observed in MC, but nonspecific cytogranules and various types of lysosomes were found more frequently than in the control (Fig. 2b).

Renin activity in the isolated glomerulus has been studied for a comparatively long time but it has been determined separately in the capillary fragment only in intact animals [5-7]; then, just as in the present case, no RA was found. The hypothesis of reserve renin production was based in particular on data showing the appearance of granules in MC during prolonged extremal stimulation of JGA. In the present experiments the appearance and rise of RA in the capillary fragment corresponded to activation and subsequent intensification of synthesis and secretory processes in MC, despite the fact that no granules were found. This morphological picture is characteristic of endocrine cells of granular type at a time of high hormone demand, when the hormone is secreted with by-passing of the stage of packing into granules, as has been shown for JGC [11]. Intensification of secretory processes in MC without granule formation has been observed in acute glomerulonephritis and in hypertensive nephropathies in man [8], but in chronic glomerulonephritis [10] and in advanced sclerosis of the kidney [1] no granules were found in MC. It is interesting to note that during constriction of the renal artery in rabbits granulation of MC was observed in the early stages after the operation [8], whereas it was absent in dogs even 5 months after the beginning of the experiment [9]. In the light of these and the present observations it seems that early granulation of MC may exhibit species differences. Its absence in the early stages may also be connected with the intensity of the secretory phase. These arguments, as well as morphological data in the literature on the similarity between JGC and MC in certain situations, suggest that the source of renin in the capillary fragment is the MC themselves. Besides them, there are only endothelial cells and podocytes in this region, and their participation in renin synthesis can be ruled out.

Renin production in MC in this situation would appear to be a reserve function, for because of constriction of the aorta the filtration pressure is not compensated by increased renin production in JGC, and the angiotensin formed in the glomerulus acts on the contractile structures of the glomerulus, compensating to some extent the filtration function of the nephron.

Renin production in MC, incidentally, also takes place in the phase of lowering of the arterial pressure, when the production of this substance in JGC is reduced. Under these circumstances there was negligible difference in RA in the capillary fragments of the rats of the first and second groups. The reason for this phenomenon is not clear and further investigation is needed.

The investigation thus showed that during prolonged disturbance of the filtration function of the kidney as a result of a reduction in the blood flow the MC become capable of producing renin and they can be regarded as reserve cells of the JGA.

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BIOSYNTHESIS OF RENAL PROSTAGLANDINS IN SPONTANEOUSLY HYPERTENSIVE RATS

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The biosynthesis of prostaglandins (PG) E_2 and $F_{2\alpha}$ from [^{14}C]arachidonic acid by renal medullary tissue of rats with spontaneous hypertension and of normotensive Wistar rats was investigated at different ages (1.5 and 3.5 months). In animals with spontaneous hypertension the synthesis of PG E_2 from arachidonic acid was at a much lower level than in Wistar rats. The biosynthesis of PG $F_{2\alpha}$ in these animals was virtually indistinguishable from normal. No age differences were found in PG formation by the kidneys of rats with spontaneous hypertension, whereas in Wistar rats PG E_2 biosynthesis was depressed at the age of 3.5 months.

KEY WORDS: prostaglandins; hypertension.

Considerable attention has recently been paid to the prostaglandins (PG), biologically active substances of lipid nature [3]. It has now been shown that PG play an important role in arterial hypertension [3, 5, 8, 9, 11], but the mechanisms of their participation in this process have not yet been explained. The question of ontogenetic variations in the biosynthesis of renal PG both under normal conditions and in arterial hypertension likewise has not been settled.

It was accordingly decided to study the biosynthesis of PG E_2 and $F_{2\alpha}$ in the renal medulla of rats with spontaneous hypertension (SHR) from exogenous [^{14}C]arachidonic acid during ontogenetic development.

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