

# DYNAMICS OF RENIN PRODUCTION BY THE JUXTAGLOMERULAR AND MESANGIAL CELLS OF SINGLE RAT GLOMERULI AFTER ADRENALECTOMY

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Six weeks after adrenalectomy rats without compensatory salt and hormones developed adrenal insufficiency, the renin activity in individual fragments of isolated glomeruli containing juxtaglomerular cells (JGC) was increased on average by 1.5 times, and renin-like activity (RLA) was found in fragments containing mesangial cells (MC). Signs of increased renin secretion (a decrease in the number of granules, marked development of the granular endoplasmic reticulum, Golgi complex, and microtubules) were observed in JGC. The corresponding organoids in MC were well developed but no granules were found. After 8-12 weeks, on restoration of the 11-HCS and sodium levels in the plasma, renin activity was restored to normal in JGC, RLA disappeared in MC, and both types of cells recovered their original ultrastructure. The reserve role of MC as a source of renin-like substances was confirmed.

**KEY WORDS:** renin; juxtaglomerular apparatus; mesangial cells; adrenalectomy; body reserves.

In certain experimental and clinical situations the function of the juxtaglomerular cells (JGC) is subject to stress. To ensure the production of large quantities of renin, the juxtaglomerular apparatus must evidently possess reserve structures. The suggestion that mesangial cells (MC) may perform this role [4] has been confirmed by chronic experiments with ischemia of the kidney [6]. If this is a truly reserve function, it ought to be manifested under various experimental conditions. The writers have found renin-like activity (RLA) in these cells 5 weeks after adrenalectomy [7]. In the present investigation the dynamics of this phenomenon was examined over longer periods of observation.

## EXPERIMENTAL METHOD

Wistar rats of both sexes weighing 180-230 g were adrenalectomized in one stage and thereafter kept on the ordinary animal house diet and given tap water to drink without any hormonal replacement therapy. The survival rate of the animals in the course of the experiments was about 90%. Intact animals served as controls. The experimental animals were killed during the first 6 weeks after the operation at weekly intervals and subsequently 2 and 3 months after the beginning of the experiments. Single glomeruli were isolated from the left kidney and separated by microdissection into arteriolar (where the JGC are located) and capillary (where the MC are located) fragments, and renin activity was determined in each of them. In parallel experiments material was taken for electron-microscopic observations and the blood pressure was measured in the carotid artery [5, 6]. The levels of sodium and potassium (by flame photometry), aldosterone (by a radioimmunologic method using kits from the firm SEA-IRE-Sorin, France), and 11-hydroxycorticosteroids (11-HCS) (fluorometrically) in the blood plasma were determined.

## EXPERIMENTAL RESULTS

In the first 3 weeks after the operation the typical picture of corticoid insufficiency developed: a fall in the concentrations of 11-HCS and sodium, disappearance of aldosterone, lowering of the blood pressure, and an increase in the potassium concentration (Fig. 1). The blood pressure and potassium level later returned to normal but the remaining parameters still remained depressed until 6 weeks after the operation, and aldosterone was virtually indeterminable. Renin activity (RA) in the arteriolar fragment was increased 1 week

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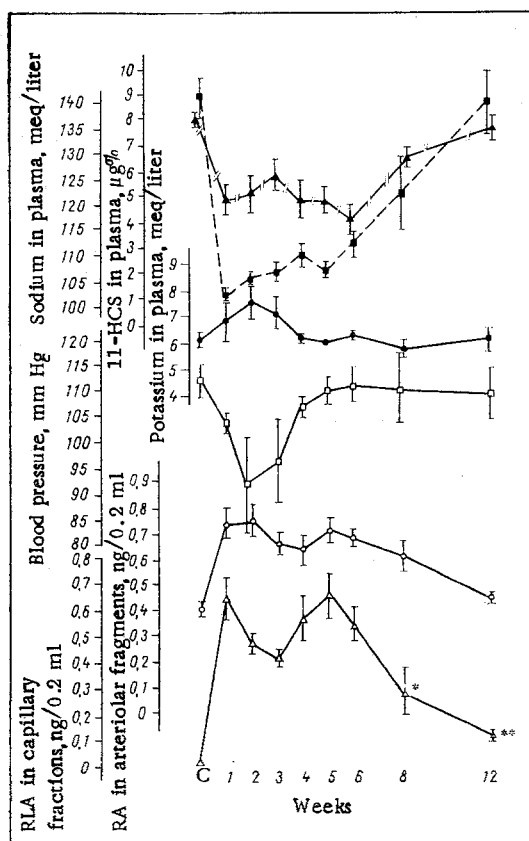


Fig. 1. Dynamics of physiological indices during experiment. Filled symbols indicate plasma concentrations of: 11-HCS (squares), sodium (triangles), and potassium (circles); empty symbols denote blood pressure (squares), RA in arteriolar fragments (circles), and RLA in capillary fragments (triangles). C) Control, \*) RLA found in 40% of samples, \*\*) RLA found in 15% of samples.

after the operation on average by more than 1.5 times, but besides increased RA, in some samples RA was below the control value. In the next 5 weeks its mean level remained about the same (Fig. 1), but marked polymorphism of the JGC was characteristically found: Some cells had a reduced number of granules and a moderately well marked granular endoplasmic reticulum (GER) and Golgi complex, whereas in other JGC there were absolutely no granules but marked hypertrophy and hyperplasia of these organelles and the development of microtubules was found. Other workers [8,12] observed the same picture in an experiment lasting 6 days. The morphology of cells of this last type is evidence that they were in a state of intensive secretion but without the phase of concentration of the hormone into granules, as is confirmed by evidence in the literature of a sharp increase in the plasma RA and a decrease in the juxtaglomerular index in the experimental model used [10,13]. These differences in the ultrastructure of JGC intensified toward the 6th week after the operation (Fig. 2a).

In the capillary fragment containing MC, RLA was found 1 week after the operation, and during the first 5 weeks it remained at about the same level. In their ultrastructure the MC resembled degranulated JGC: They contained an increased number of cross-sections of GER and Golgi complex, especially 4-6 weeks after the operation, and microtubules appeared. Hyperplasia of the mitochondria was observed and polysomes, lysosomes, and cytoplasmic granules of lysosome-like type were found more often than normally (Fig. 3a). Characteristically in the ischemic kidney, as studied previously [6, 7], MC had the same ultrastructure at times when RLA could be found in the capillary fragment. The relatively later (than 3-4 weeks after the operation) appearance of RLA in this model was attributed to the weaker activity of the JGC than after adrenalectomy [7]. Intensive synthesis and secretion of renin-like substances, proceeding without the phase of granule formation, may be considered to have taken place in MC in the present experiments also.

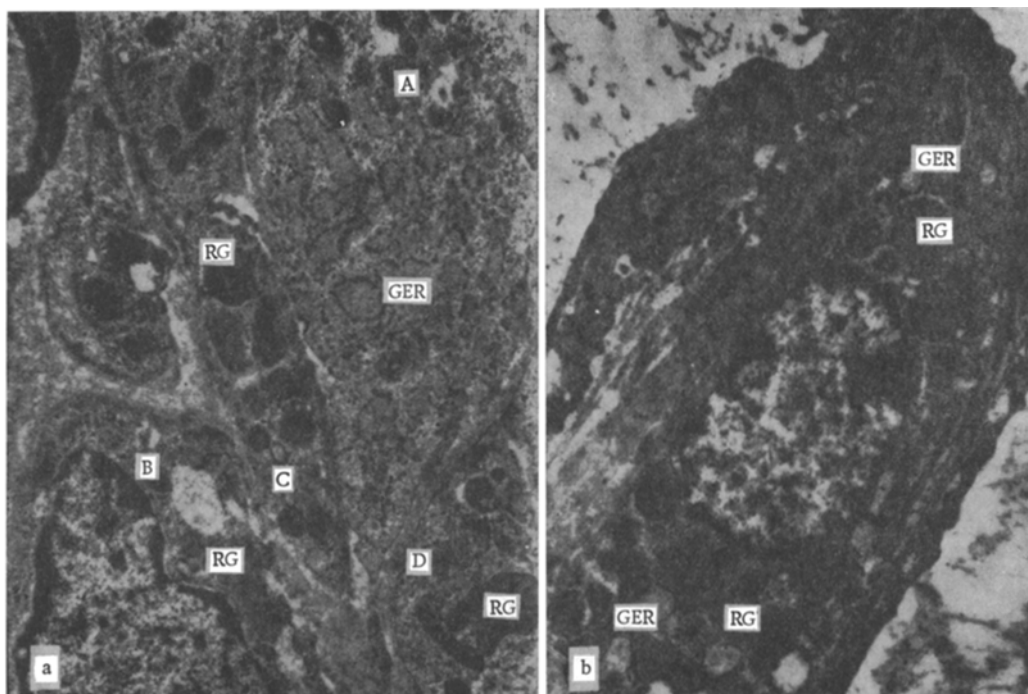


Fig. 2. Ultrastructure of juxtaglomerular cells: a) 6 weeks after operation; fragment of cell A: marked hyperplasia of elements of GER with appearance of electron-dense contents in lumen; fragments of cells B, C, and D: decrease in number and polymorphism of renin granules ( $\times 14,100$ ); b) 12 weeks after operation: restoration of normal number and appearance of granules, GER moderately developed ( $\times 9880$ ); RG) renin granules.

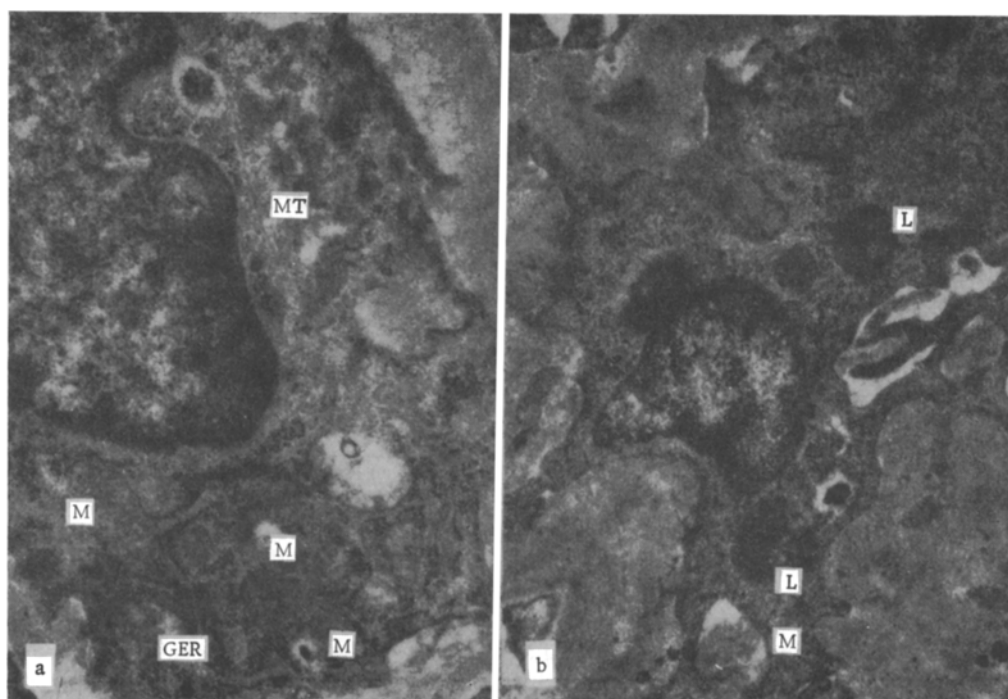


Fig. 3. Ultrastructure of mesangial cells: a) 5 weeks after operation: intensified development of GER with increased number of ribosomes on its membranes, hyperplasia of mitochondria and microtubules ( $\times 31,200$ ); b) 12 weeks after operation: restoration of normal cell ultrastructure, but number and size of lysosomes increased ( $\times 21,500$ ). M) Mitochondria, L) lysosomes, MT) microtubules.

In the 6th-12 week after the operation gradual restoration of the 11-HCS and sodium concentrations in the plasma was observed (Fig. 1). Without attempting to discuss the possible reserve sources of 11-HCS here, it can be stated that these hormones restore the plasma sodium level in adrenalectomized animals [3]. In this connection, activation of JGC induced at the beginning of the experiment ought to have decreased, despite the continued absence of aldosterone. In fact, during this period RA in the arteriolar fragments fell to the control values, and in JGC there was a tendency toward return to the original state (Fig. 2b), with a decrease in the number of agranular cells, RLA in the capillary fragments fell progressively almost to zero (Fig. 1), and in MC the degree of development of organoids of synthesis and secretion was reduced (Fig. 3b). Most MC reverted to their original state, except that lysosomes were more numerous and larger than normally. Just as in ischemia of the kidney [6], no organelles were found that could be reliably identified as renin granules, although in one MC 2 months after the operation structures similar to them in morphology were found.

Some investigators [1, 2, 9] noted the appearance of two to four granules in MC which they concluded were renin granules, 7, 25, and 75 days after adrenalectomy. These granules were morphologically similar to some of the cytoplasmic particles found in MC in the present investigation and identified as nonspecific, for they appeared to be lysosomes at different stages of development. The problem of the renin nature of the granules in MC at these times after adrenalectomy cannot be regarded as solved. True renin granules in MC have been demonstrated only in long-term investigations (6 months) on cats [11] treated with glucocorticoids. The duration (3 months) of the present investigation was perhaps too short for renin to appear in MC in the granular form. Consequently, RLA in the capillary fragment was found much sooner than granules could have appeared in MC.

This investigation thus confirms the reserve role of MC in the production of renin-like substances in the presence of yet another type of load on JGC, namely in corticoid insufficiency.

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