MORPHOLOGY AND PATHOMORPHOLOGY

Morphological Peculiarities of Juxtaglomerular Apparatus of the Kidney in Rats with Hereditary Stress-Induced Arterial Hypertension (NISAG Rats)

N. P. Kazarinov, M. D. Shmerling, A. L. Markel', and G. S. Yakobson

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 127, No. 5, pp. 576-579, May, 1999
Original article submitted July 16, 1998

Structure of juxtaglomerular apparatus of the kidney in NISAG rats and morphometric parameters of renin-producing juxtaglomerular cells of afferent arterioles attest to its activation.

Key Words: *heredity; stress; hypertension; kidneys; juxtaglomerular apparatus*

According to current views, essential hypertension is determined by hereditary factors, but realization of this pathology largely depends on environmental factors, in particular emotional stress [5,9].

Recent progress in understanding the etiology and in improving the therapy and prevention of essential hypertension is associated with further experiments on animals models of hypertension [1]. In new model created at the Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Sciences, hypertension develops under the effect of an emotional stress and is determined by hereditary hypersensitivity to stress (NISAG rats — rats with hereditary stress-induced hypertension) [11]. Hypertension in these rats develops progressively and its dynamics corresponds to that in humans.

Kidneys play a central role in the pathogenesis of hypertension. It is generally accepted that kidneys maintain established hypertension. On the other hand, some data suggest that kidney abnormalities are primary in hypertension [10,12]. Among kidney structures involved in the regulation of blood pressure, of particular interest are juxtaglomerular (JG) apparatus (JGA) and its components renin-producing JG cells. Functional activity of JGA can be assessed by certain morphological criteria [2]. The present study was aimed at revealing morphological signs of hyperactivation of JGA in NISAG rats and evaluation of its role in the development of hypertensive status of the renin-angiotensin system in these animals.

MATERIALS AND METHODS

Experiments were carried out on six 6-month-old male NISAG rats weighing 370±17 g. Control group comprised 5 normotensive male Wistar rats weighing 395±21 g. The animals were sacrificed under ether anesthesia. Kidney tissue was fixed for electron microscopy using standard methods and embedded in Epon-Araldite. Semithin sections were stained with toluidine blue, methylene blue, and azur II-fuchsin. These preparations were examined under a light microscope and selected material was used for preparation of ultrathin sections (examined under a JEM-100SX electron microscope).

A total of 26 afferent arterioles of NISAG rats and 54 arterioles of Wistar rats were analyzed morpho-

Laboratory of Electron Microscopy, Institute of Physiology, Siberian Division of the Russian Academy of Medical Sciences, Institute of Cytology and Genetics, Siberian Division of the Russian Academy of Sciences, Novosibirsk

0007-4888/99/0005-0522$22.00

metrically. The structures for morphometric analysis were selected as described previously [2,4]. In each arterioles 2-15 JG cells were analyzed. Only cells containing renin granules occupying no less than 2% cytoplasm were taken into account. Primary morphometric data were averaged for each arteriole. The significance of differences was verified using the Student *t* test.

RESULTS

Plain light microscopy of the renal cortex revealed no marked changes of JGA in experimental animals. The number of granular cells greatly varied within the same rat group and between strains. Large JG cells with multiple renin granules were seen in the afferent

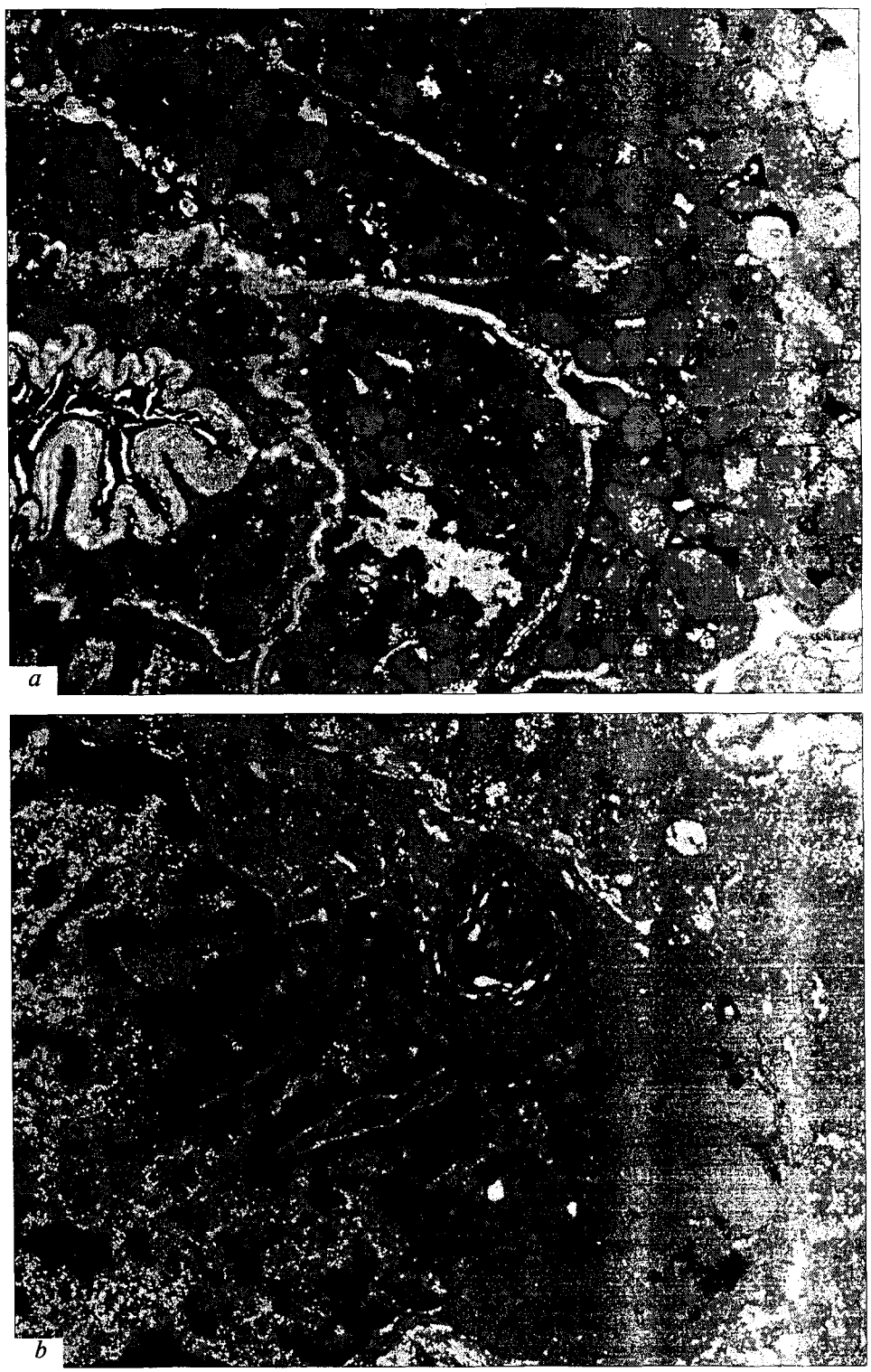

Fig. 1. Fragment of renal glomerulus (*a*) and afferent arteriole (*b*) of NISAG (*a*) and Wistar rats (*b*). *a*) juxtaglomerular cell contains many renin granules, ×16,000; *b*) juxtaglomerular cell contains renin granules and a large residual body, ×20,000.

TABLE 1. Relative Volume of Organels (%) in Cytoplasm of JG Cells (*M±m*)

Structures	Wistar rats	NISAG rats
Renin granules	36.87±2.44	34.95±5.25
Granular endoplasmic reticulum	2.26±0.29	4.58±1.14*
Mitochondria	4.51±0.25	6.84±0.93**
Golgi apparatus	0.72±0.16	0.86±0.30
Residual bodies	0.30±0.18	0.04±0.03

Note. *$p<0.05$, **$p<0.01$ compared with the control.

arterioles in both Wistar and NISAG rats. However, in some NISAG rats a layer of granular JG cells extended from glomerulus to interlobular artery.

Under electron microscope, the most pronounced changes in JGA were seen in JG cells of the afferent arteriole. We concentrated on these cells since they play a crucial role in renin production.

In JG cells of Wistar rats renin granules usually occupied about 30% cytoplasm. In NISAG rats JG cells were characterized by marked polymorphism: from hypo- to hypergranular forms (Fig. 1, *a*). The mean percentage of granulation (with regard for selection criteria) was practically the same in both animal strains (Table 1).

The content of renin granules in JG cells to a certain extent depends on selection criteria. Preliminary estimation of the mean number of renin granules in the cytoplasm of all types of JC cells yielded values close to published data (about 30-33%).

However, this criterion can not be used for NISAG rats, because of the presence of cells with high myofilaments content and solitary renin granules. These cells had more developed protein-synthesizing apparatus than typical smooth muscle cells. We proposed that this phenomenon reflects initial transformation of smooth muscle cells into JG cells (transition cells) in NISAG rats. Similar changes accompany JGA activation in renovascular hypertension [3].

Taking into account cells polymorphism in afferent arteriole wall in NISAG rats, selection criterion was the presence of renin granules occupying no less than 2% cytoplasm. This approach overestimated the content of renin granules in JG cells of both animal strains by about 12%, but eliminated the influence of transition cells, which appeared in case of activation of JGA. This approach seems to be quite applicable for comparison of these animal groups.

It has been previously shown that hyperfunction of JGA is accompanied by hyperplasia of JG cells and hypertrophy of the granular endoplasmic reticulum and Golgi complex, rather than increased content of renin granules [3].

Morphometric analysis revealed high biosynthetic activity of JG cells in NISAG rats, in particular, a great number of mitochondrial profiles per standard cytoplasm area (3.02±0.41 vs. 2.19±0.17 per μ^2 in Wistar rats, $p<0.05$) and a large relative volume of granular endoplasmic reticulum, mitochondria and Golgi apparatus (Table 1).

Residual bodies were often present in JC cells of Wistar rats. The relative volume of residual bodies in the cytoplasm and statistical processing of morphometry data revealed no significant differences between groups, but this can be attributed to relatively rare occurrence of residual bodies in sections and insufficiency of experimental data (Table 1).

Accumulation of residual bodies in the cytoplasm can be related to enhanced metabolic activity [8]. At the same time, secretory granules in endocrine cells, if not utilized for a long time, can be degraded by lysosomal enzymes. This mechanism improves safety of the system [6,7]. A lower relative volume of residual bodies in NISAG rats probably results from enhanced renin release from JG cells, when secretory granules are not stored for a long time and not degraded by lysosomal enzymes (Fig. 1).

We found no publications describing the distribution of residual bodies in JG cells depending on JGA activity. Apparently, this parameter should be taken into account when studying morphological equivalents of JGA function.

Thus, structural features of JGA and morphometric parameters of JG cells suggest activation of JGA in NISAG rats.

Unlike many other experimental models of hypertension and JGA hyperactivation, hypertension in NISAG rats is not accompanied by marked hyperplasia of JGA and accumulation of biosynthetic organelles in JG cells; it is more natural and the main changes are observed at the ultrastructural, but not at the light microscopic level.

Comparison of our findings with published data allows us to conclude that changes in JGA in NISAG rats correspond to JGA alterations typical of "mild benign hypertension in humans".

REFERENCES

1. R. J. Geller, J. S. Mac-Giff, Arterial Hypertension [in Russian], Eds. I. K. Shkhvatsabaya and J. H. Lahr. Moscow (1980), pp. 101-109.
2. M. A. Pal'tsev, *Arkh. Pat.*, **49**, No. 1, 62-66 (1987).
3. Yu. L. Perov, *Functional Morphology of the Kidney in Experimental Essential Hypertension*, Abstract of Doct. Med. Sci. Dissertation, Moscow (1981).
4. Yu. L. Perov, *Arkh. Pat.*, **46**, No. 7, 78-84 (1984).
5. K. V. Sudakov, *Systemic Mechanisms of Emotional Stress* [in Russian], Moscow (1981).

6. V. I. Fedorov, *Uspekhi Sov. Biol.*, **105**, No. 2, 231-251 (1988).
7. A. M. Fedotov and V. I. Fedorov, *Cybernetic Models in Biology* [in Russian], Novosibirsk (1974), pp. 167-178.
8. Yu. S. Chentsov, *General Cytology* [in Russian], Moscow (1995).
9. I. K. Shkhvatsabaya, *Kardiologiya*, **25**, No. 6, 5-12 (1985).
10. E. Guidi, D. Menghetti, S. Milani, *et al.*, *J. Am. Soc. Nephrol.*, **7**, No. 8, 1131-1138 (1996).
11. A. L. Markel, *Genetics of Hypertension*, Ed. J. S. Sasard, Paris (1992), pp. 405-407.
12. A. E. G. Raine, *Br. Med. Bull.*, **50**, No. 2, 322-341 (1994).