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CHARACTERISTICS OF INTERSTITIAL CELLS OF THE RENAL MEDULLA DURING LASIX-INDUCED STIMULATION OF PROSTAGLANDIN PRODUCTION

B. N. Salikhov and A. Khamraev

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KEY WORDS: kidney, medulla, interstitial cells, electron microscopy.

Loop diuretics, which include Lasix, have not only a direct tubular diuretic action, but also have a stimulating effect on renal prostaglandin production [2, 4, 10]. Renal prostaglandins perform the function of regulators of vascular reactions in the kidney. Under the influence of Lasix prostaglandin production is increased most strongly in the inner medullary layer of the kidneys [13]. The main sources of renal prostaglandins in this zone are the interstitial cells [2, 11, 12]. The mechanism of action of Lasix on prostaglandin synthesis in the interstitial cells is not yet clear. There have been sporadic studies of the effect of a single injection of Lasix on these cells [6]. However, in clinical practice Lasix is often used over a long period of time, and this necessitates the study of the mechanisms of its effect on the interstitial cells under conditions of long-term administration.

The aim of this investigation was to study the structural and functional state of the interstitial cells of the internal medulla of the kidneys during long-term Lasix administration.

EXPERIMENTAL METHOD

Experiments were carried out on 28 noninbred male albino rats weighing 120-150 g. All the animals were divided into three experimental groups: group 1 (n = 8) served as the control, group 2 (n = 10) received a single dose of Lasix, whereas group 3 (n = 10) received Lasix daily for 30 days. Lasix in a dose of 3 mg/kg was injected intraperitoneally. The animals of group 2 were killed 30 min after injection of the preparation. Animals of group 3 were killed 30 min after the last injection. In all the experimental groups the animals were killed by decapitation in the morning before taking food. Pieces of the inner zone of the renal medulla were fixed in 1% glutaraldehyde solution and postfixed in 1% OsO_4 solution. Both fixatives were made up in 0.1 M phosphate buffer, pH 7.4. The material was dehydrated in alcohols and acetone and embedded in Araldite. Ultrathin sections cut on the LKB-4800 ultramicrotome were stained with uranyl acetate and lead citrate and studied under the IEM-100B electron microscope.

EXPERIMENTAL RESULTS

The experiments showed that the structure of the interstitial cells in animals of the control group corresponded to existing views [1, 7-9]. These cells were oriented strictly at right angles to the longitudinal axis of the renal papilla, and were distinguished by their elongated shape and their numerous cytoplasmic processes, which made contact with surrounding structures. Many membranous organelles could be seen in their cytoplasm: the rough and smooth endoplasmic reticulum, Golgi complex, mitochondria, and lysosomes (Fig. 1a).

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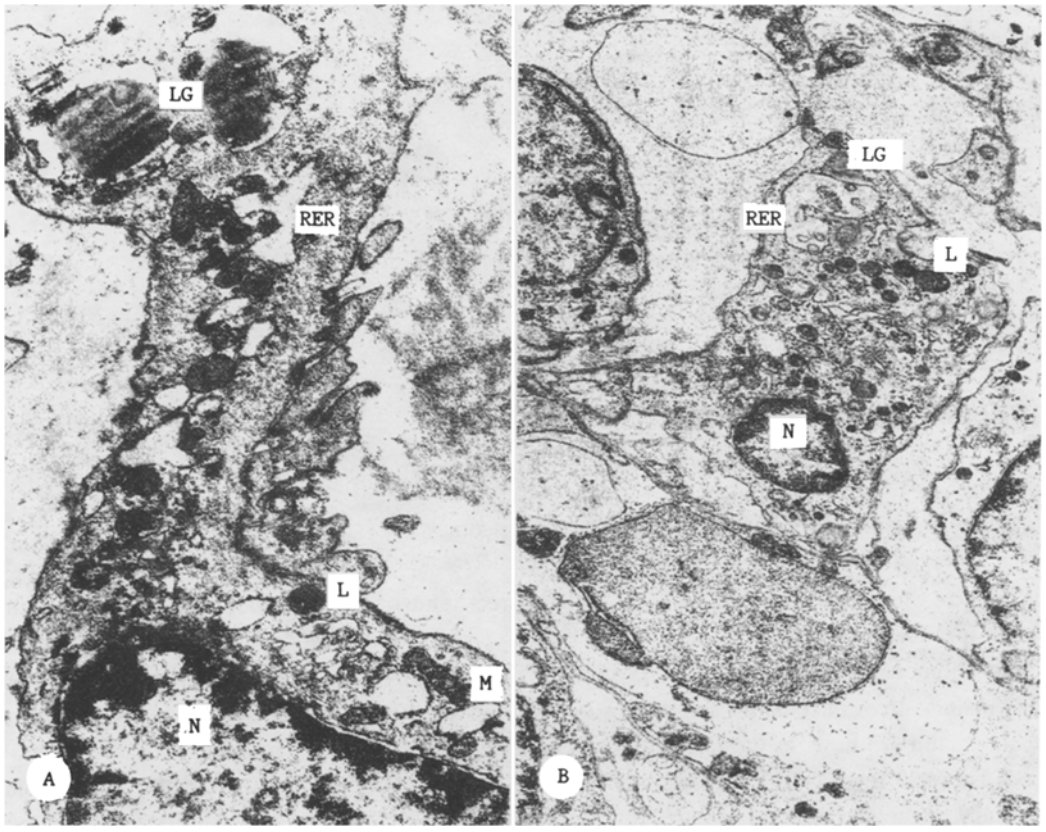

Fig. 1. Ultrastructure of interstitial cells of the renal medulla. A) Intac animals. 30,000×. B) 30 min after injection of Lasix. 20,000×; N) nucleus, M) mitochondria, L) lysosomes, LG) lipid granules, RER) rough endoplasmic reticulum.

The most specific subcellular structures of the interstitial cells are lipid granules and lysosomes. The relative proportions of these structures may serve as a criterion of the prostaglandin-synthesizing activity of the interstitial cells, i.e., an increase in the number of lysosomes together with a decrease in the number of lipid granules in the interstitial cells are evidence of activation of prostaglandin synthesis [3].

An electron-microscopic investigation of the interstitial cells 30 min after a single injection of Lasix revealed a marked increase in the number of lysosomes against the background of a sharp decrease in the number of lipid granules. Developed components of the endoplasmic reticulum and Golgi complex were seen in this case in the cytoplasm of the cells (Fig. 1b). Thus, after a single injection of Lasix, predominance of lysosomes over lipid granules could be seen in the interstitial cells against the background of developed organelles. Activation of prostaglandin production in response to a single injection of Lasix has been demonstrated also by other workers [6].

By contrast with a single injection, during long-term (30 days) injection of Lasix, two types of interstitial cells were found in the internal renal medulla. The first type was closely similar in ultrastructure to the interstitial cells described in the experimental animals of group 2. However, fewer lysosomes and lipid granules were seen in their cytoplasm than in the animals of group 2, although quantitatively speaking, lysosomes predominated in this case over lipid granules. Changes of this kind are evidence that during long-term administration of Lasix, prostaglandin production by the interstitial cells was weaker than after a single injection.

A distinguishing feature of the type 2 cells is the presence of a developed rough endoplasmic reticulum, occupying its basal part, in their cytoplasm. Lipid granules typical of interstitial cells were found in single numbers or were completely absent (Fig. 2). Close to the cells there were coarse bundles of collagen fibers, lying in the thickness of the amorphous intercellular substance (Fig. 3a, b). Meanwhile, besides the types of interstitial cells described above, no other cells could be identified in the interstitial tissue, whose structure might suggest the synthesis of intercellular components of connective tissue and, in particular, collagen fibers. On the basis of analysis of these results, we consider that some of the interstitial cells, during long-term activa-

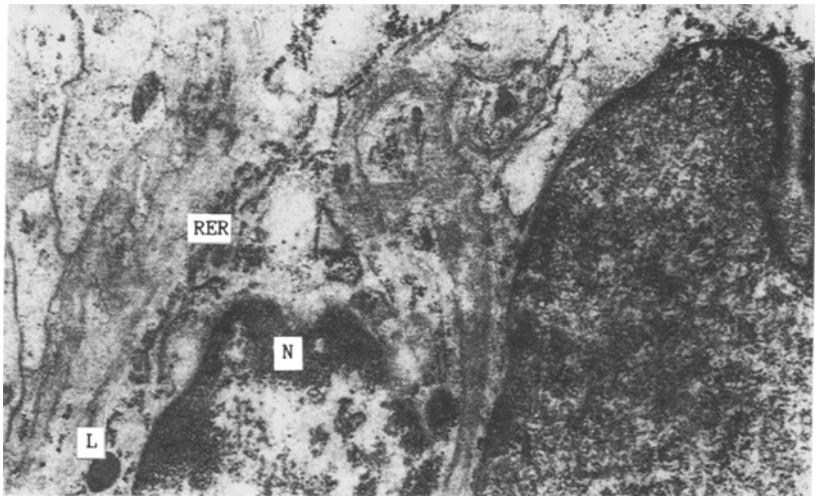

Fig. 2. Ultrastructure of type 2 interstitial cells of the renal medulla during long-term administration of Lasix. 30,000×.

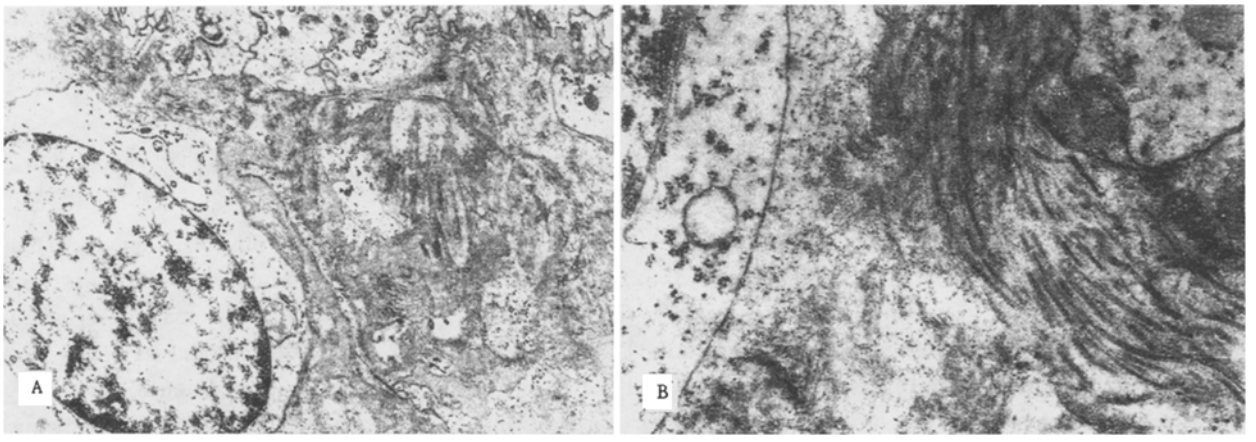

Fig. 3. Enlargement of noncellular components of connective tissue in interstitial tissue of inner zone of renal medulla during long-term injections of Lasix. A) Collagen fibers and amorphous intercellular substance. 20,000×; B) Coarse bundles of collagen fibers. 30,000×.

tion by diuretics, may switch to the production of intercellular connective-tissue components. This may evidently be one of the causes of the development of sclerosis in the renal papilla.

Thus, a single injection of Lasix stimulates prostaglandin synthesis by the interstitial cells. Long-term stimulation ultimately leads to a relative decrease of prostaglandin production in the interstitial cells, by comparison with a single injection of Lasix. Under these circumstances a second population of these cells if formed, oriented toward the production of connective-tissue proteins and glycosaminoglycans. It was suggested previously that interstitial cells, being elements of mesenchymal origin, specialized for prostaglandin synthesis, preserve their ability to produce components of the interstitial substance of the medulla [5].

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ANTICONVULSANT EFFECTS OF NEUROTROPIN

A. A. Shandra, K. V. Sudakov*, and G. N. Kryzhanovskii** UDC 615.357:577.175.829].017:615.213].076.9

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The possibility of suppressing epileptic activity by substances of endogenous origin has now been demonstrated [1, 2, 5, 6]. One preparation, obtained from rabbit skin inoculated with cowpox virus, is neurotropin, produced by the firm "Nippon Zoki Pharmaceutical Limited" [7]. Neurotropin possesses a broad spectrum of biological activity. Besides its antiallergic and anti-inflammatory action, neurotropin also affects brain function. The antistressor action of neurotropin and its beneficial effect in experimental cerebral edema in mice have been established [11]. Neurotropin acts selectively on brain electrical activity [6].

The aim of this investigation was to study the effects of neurotropin on generalized and local forms of epileptic activity induced in animals of different species (rats, mice, cats).

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats (270-320 g), C5BF6 mice (18-22 g), and cats (2.5-3.2 kg) under acute conditions. Seizures were induced by intraperitoneal injection of picrotoxin ("Serva," West Germany) 4.0 mg/kg, bicuculline ("Serva") 4.0 mg/kg, metrazol 60 mg/kg, or kainic acid ("Sigma," USA) 15 mg/kg. Seizures were recorded visually for 1 h after the injection of the convulsants. The latent period of the first seizures, their maximal intensity, and the number of animals developing seizures were determined. The intensity of the seizures was estimated by the use of a five-point scale [4]. Foci of epileptic activity were induced by application of a piece of filter paper (2 × 2 mm), soaked in 0.1% strychnine nitrate, to the cerebral

*Academician of the Academy of Medical Sciences of the USSR.
**Academician of the Academy of Medical Sciences of the USSR.

Department of Normal Physiology, N. I. Pirogov Odessa Medical Institute. Department of Normal Physiology, I. M. Sechenov First Moscow Medical Institute. Laboratory of General Pathology of the Nervous System, Research Institute of General Pathology and Pathophysiology, Academy of Medical Sciences of the USSR, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 111, No. 1, pp. 49-52, January, 1991. Original article submitted July 10, 1990.

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