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STATE OF THE JUXTAGLOMERULAR APPARATUS AND INTERSTITIAL CELLS OF THE RENAL MEDULLA AFTER ADMINISTRATION OF CERTAIN DRUGS AND HYPERBARIC OXYGENATION

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The arsenal of drugs available for treatment of diseases of the kidneys is growing continually. However, many mechanisms of the action of these drugs on renal function still remain unexplained. Recent investigations have shown that the action of most of them is aimed at redistribution of the blood in the kidneys. In this connection data have been published on the action of drugs on the juxtaglomerular apparatus (JGA) and insterstitial cells (IC). In particular, an increase in renin activity (RA) in the blood plasma has been demonstrated after administration of frusemide [2]. This effect is explained by the direct action of frusemide on the dense spot of the JGA [10]. Meanwhile the excretion of prostaglandin (PG) E with the urine is increased [8]. Indomethacin, an inhibitor of prostaglandin synthetase, reduces the synthesis of PG A and E and also reduces RA in the blood plasma [9]. Under these circumstances the blood flow in the kidneys is redistributed from the inner zone of the cortex to the outer zone [5]. During hyperbaric oxygenation (HBO) sodium reabsorption and oxygen consumption are reduced. Urine containing a high concentration of sodium acts on the dense spot, increasing activity of the JGA and RA [7]. Venoruton, which belongs to the flavnoid group, reduces capillary permeability and improves the venous drainage. The action of trental is connected with inhibition of cyclic AMP phosphodiesterases [4]. The action of these last two drugs on the renin–angiotensin and prostaglandin systems of the kidneys is unknown. Changes in JGA and IC under the influence of all the drugs mentioned above have virtually not yet been investigated. Only the effect of indomethacin on the JGA and IC is well known [3, 6].

The object of the present investigation was to study the state of the JGA and IC after administration of a series of drugs widely used in the treatment of kidney diseases, and also after exposure to HBO.

EXPERIMENTAL METHOD

Experiments were carried out on 42 rabbits, divided into 11 experimental groups with three to six animals in each group. The control group contained six animals. Frusemide in a dose of 20 mg/kg, indomethacin 10 mg/kg, venoruton 500 mg/kg, and trental 100 mg/kg were injected intravenously into rabbits of the appropriate groups. Other rabbits were exposed to HBO (1, 6, and 12 sessions) on alternate days under a pressure of 0.5 atm. The rabbits were killed either 3 h (the time for the drug to accumulate in the organ) or 24 h (the time of its excretion from the body) after injection of the drugs. Pieces from the outer zone of the cortex and inner zone of the medulla (papilla) of the kidneys were fixed in 1% OsO_4 solu-

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TABLE 1. Number of Lipid Granules in Cytoplasm of IC and Density of Granules (T) in JGA after Administration of Frusemide, Indomethacin, Venoruton, and Trental and Exposure to HBO (M ± m)

Treatment	Dose	Time of sacrifice of animals after treatment	Number of granules in cytoplasm of IC	Density of granules (T) in epithelioid cells of JGA
Frusemide	20 mg/kg	3 h	5,62 ± 0,23	0,61 ± 0,04
		24 h	7,19 ± 1,42	0,49 ± 0,03
Indomethacin	10 mg/kg	3 h	6,58 ± 1,07	0,53 ± 0,05
		24 h	4,57 ± 0,13	0,30 ± 0,03
Venoruton	500 mg/kg	3 h	5,66 ± 0,37	0,64 ± 0,06
		24 h	5,33 ± 0,25	0,55 ± 0 05
Trental	100 mg/kg	3 h	6,38 ± 0,30	0,60 ± 0,01
		24 h	6,27 ± 0,36	0,58 ± 0,02
HBO	0,5 atm	1 session	3,37 ± 0,51	0,29 ± 0,05
		6 sessions	3,79 ± 0,31	0,71 ± 0,03
		12 sessions	6,48 ± 0,19	0,73 ± 0,03
Control	—	—	4,91 ± 0,25	0,71 ± 0,10

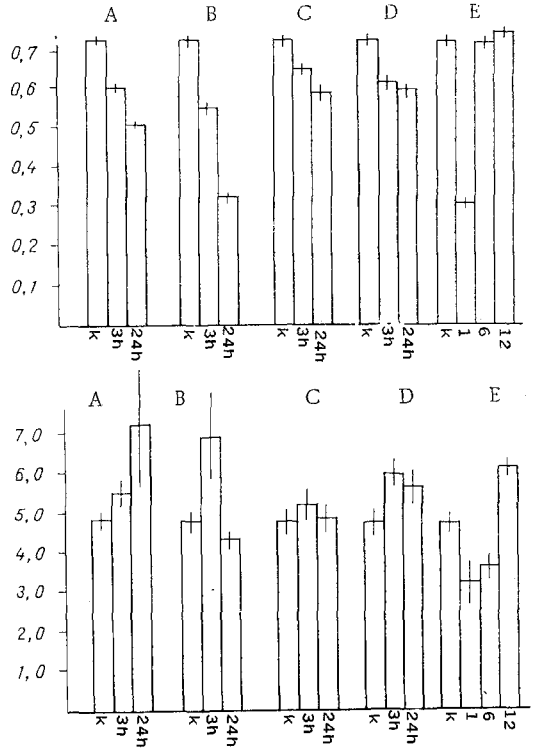

Fig. 1. Change in density of granules in epithelioid cells of JGA after administration of frusemide (A), indomethacin (B), venoruton (C), trental (D), and after exposure to 1, 6, and 12 sessions respectively of HBO (E). Here and in Fig. 2: K) control.

Fig. 2. Changes in number of granules in IC of renal medulla after administration of frusemide (A), indomethacin (B), venoruton (C), and trental (D) and after exposure to 1, 6, and 12 sessions respectively of HBO (E).

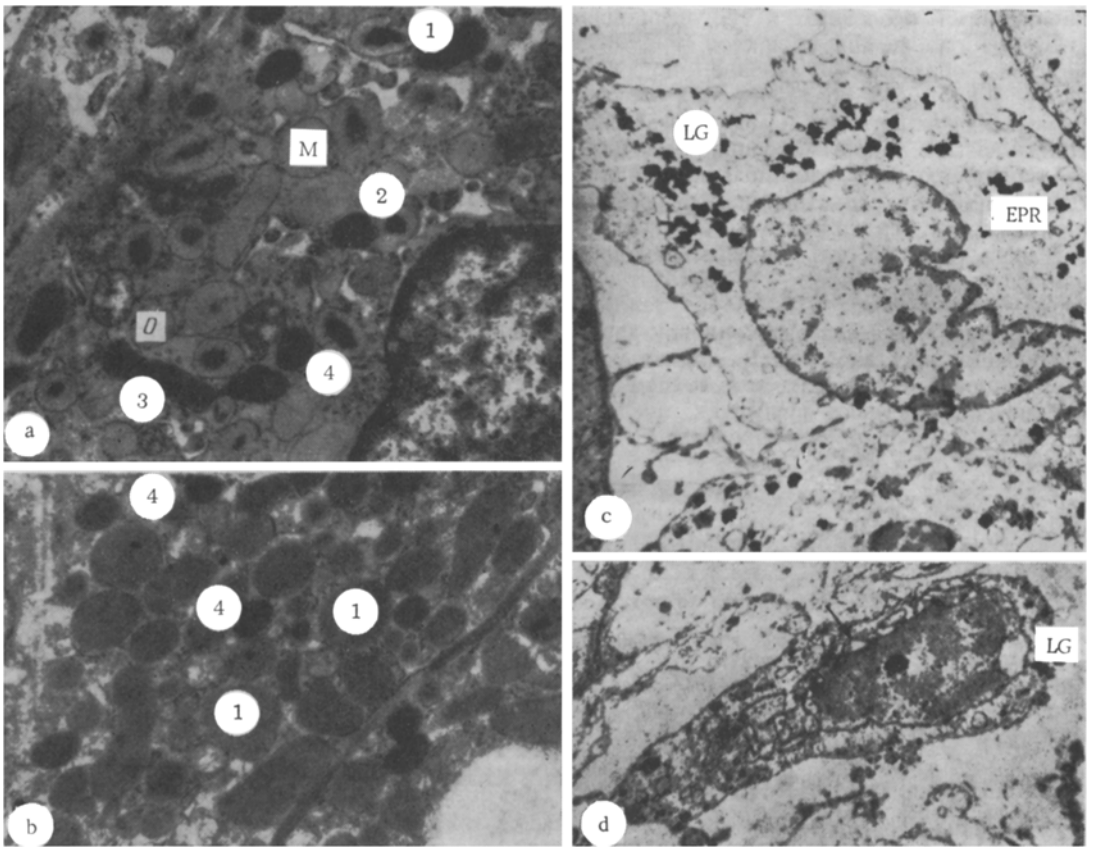

Fig. 3. Changes in JGA and IC after administration of indomethacin and frusemide and after exposure to HBO: a) epithelioid cell of JGA 24 h after injection of indomethacin: 1-4) granules of types 1, 2, 3, and 4 respectively in cytoplasm. M) Membranes of granules without contents, 10,000 ×; b) granules of types 1 and 4 (1 and 4 respectively) in cytoplasm of epithelioid cell of JGA 24 h after administration of frusemide, 14,000 ×; c) accumulation of lipid granules (LG) and hyperplasia of endoplasmic reticulum (EPR) in cytoplasm of IC of renal medulla 3 h after administration of frusemide, 5000 ×; d) vacuolation of perinuclear space and reduction of outgrowths of IC (arrows) after six sessions of HBO, 4000 ×.

tion, dehydrated in alcohols of increasing strength, and embedded in Araldite. Lipid granules in IC were counted in semithin Araldite sections stained with methylene blue—azure II—fuchsin. JGA activity was estimated by electron-microscopic analysis using a technique developed by ourselves. Four types of granules were distinguished in the epithelioid cells of the JGA during the electron-microscopic investigation: type 1) granules with relatively translucent contents; type 2) granules with small electron-dense areas in the matrix; type 3) electron-dense granules surrounded by a thin pale border, type 4) uniformly electron-dense granules. To describe each type of granule objectively, a rating coefficient was used: $K_1 = 0.1$, $K_2 = 0.5$, $K_3 = 0.6$, $K_2 = 1.0$. The granule density coefficient (T) was calculated by the equation:

$$T = \frac{\sum_{i=1} K_i n_i}{\sum_{i=1} n_i},$$

where n is the number of granules assessed. Analysis of the values of the coefficient shows that the closer it was to unity, the more mature electron-dense granules (type 4) were present in the JGA.

EXPERIMENTAL RESULTS

The number of immature granules with low electron density in the epithelioid cells of the JGA was increased 3 h after administration of frusemide. Even more such granules were pres-

ent after 24 h. Similar patterns were found after administration of indomethacin, trental, and venoruton (Table 1). After HBO the number of immature granules in JGA increased on the whole, especially after one session of HBO. Differences after 6 and 12 sessions, however, were not significant (Fig. 1). Lipid granules accumulated in the cytoplasm of IC after frusemide, especially 24 h after its administration. When indomethacin was given, on the other hand, initial accumulation of granules was followed by a decrease in their number below the control level. Their number fell after administration of trental and venoruton, but still remained above normal. The initial decrease in the number of granules in IC after one and six sessions of HBO was replaced by an increase in their number above the control level after 12 sessions (Table 1; Fig. 2).

Electron-microscopic analysis of the state of the JGA and IC also showed that granule formation processes were significantly changed by the action of the drugs in cells synthesizing renin and PG. For instance, 3 h after injection of indomethacin immature granules of types 1 and 2 predominated in the epithelioid cells of the JGA, and because of the rapid emptying of the granules, it was even possible to observe their membranes with electron-transparent contents. Hyperplasia of the endoplasmic reticulum and lamellar complex was discovered at the same time. After 24 h the number of "empty" granules in the JGA increased still more (Fig. 3a). Meanwhile, under the influence of frusemide, the mature granules disappeared practically completely, and granules with average density (type 1) predominated (Fig. 3b). During accumulation of granules in IC after administration of frusemide, the number of granules in some IC increased, whereas their number in other IC remained unchanged or actually decreased (Fig. 3c). The decrease in the number of granules in IC during HBO could be connected with degenerative changes in the cells and a consequent disturbance of synthetic processes (Fig. 3d).

Electron-microscopic analysis of the JGA and IC after administration of drugs used in the treatment of kidney diseases thus indicates the qualitatively different character of the change in granule formation (for example, the action of indomethacin and frusemide on the JGA). Quantitative analysis of the granules in IC reveals how under the influence of drugs affecting the blood flow some inhibition of the liberation of PG from their depots (granules in IC) takes place, and is expressed as the accumulation of granules followed by restoration of their normal number after elimination of the drug (frusemide, administration of which was followed by accumulation of the granules for 24 h, constituted the exception).

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