ROLE OF THE INTERSTITIAL CELLS IN PROSTAGLANDIN SYNTHESIS IN THE RENAL MEDULLA

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An electron-microscopic investigation was made of the interstitial cells of the renal medulla after injection of indomethacin, an inhibitor of prostaglandin synthesis, into rats. The number of lipid granules in the interstitial cells was greatly increased under these circumstances. This fact demonstrates the participation of lipid granules in the synthetic function of the interstitial cells as reserve depots for chemical precursors of the prostaglandins, synthesized by the interstitial cells.

KEY WORDS: interstitial cells of the kidneys; lipid granules; prostaglandins; indomethacin.

In the modern view the antihypertensive function of the kidneys is a collective concept which includes, besides other factors, the production of depressor and antihypertensive substances of varied nature by the renal medulla. Chemical analysis of extracts of the medulla, possessing a marked depressor action, has shown the presence of a wide spectrum of substances of lipid nature. Some of them have been identified as neutral lipids [8], whereas others are a complex of unsaturated fatty acids identified as prostaglandins of the E, A, and $F_{2\alpha}$ types [7].

Experiments with a pure culture of interstitial cells showed that it is very likely that the interstitial cells are the site of synthesis of renal prostaglandins [9]. However, the mechanism of this synthesis has not yet been explained and the secretory activity of the cells awaits evaluation.

However tempting it might be to link the functional activity of the interstitial cells with the number of lipid granules, no direct proof has been obtained of such a relationship.

The decrease in the number of lipid granules can only tentatively be correlated with the intensity of prostaglandin synthesis and with the utilization of the material of the granules, namely arachidonic acid, for this synthesis. This idea has been used to assess the results of a number of investigations carried out at the Institute of Cardiology [1-4].

Many papers on specific inhibitors of prostaglandin synthesis have been published in recent years. Natural inhibitors of synthesis have not yet been found in the body, but there is a group of substances which can block this synthesis in vitro or in vivo. This refers to a group of substances with primarily aspirin-like and antiinflammatory action [6, 10].

The object of this investigation was to study the interstitial cells and lipid granules during administration of inhibitors of prostaglandin synthesis to animals.

EXPERIMENTAL METHOD

Two groups of male Wistar rats (20 animals) weighing 150 g were used. The animals received a standard pellet diet and drinking water ad lib. Every day 15 animals received an aqueous suspension of the

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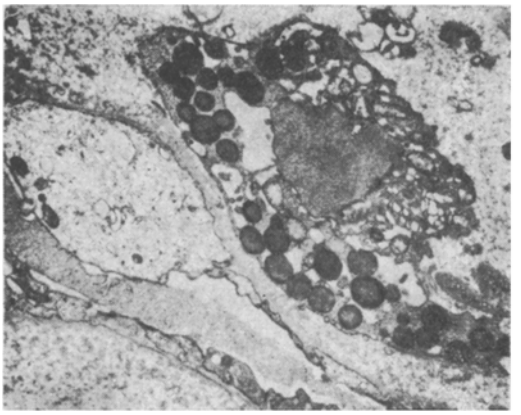

Fig. 1

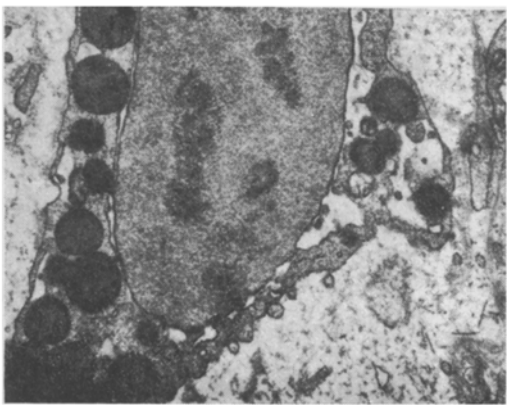

Fig. 2

Fig. 1. Interstitial cell of medulla after administration of indomethacin. Abundance of osmiophilic granules (31) in cytoplasm. Electron micrograph, 4500 ×.

Fig. 2. Interstitial cell after administration of indomethacin. Characteristic appearance of nucleus circular, with uniform distribution of chromatin in karyoplasm. Widening of perinuclear space. Electron micrograph, 12,500 ×.

drug indomethacin, a universal inhibitor of in vivo prostaglandin synthesis, by gastric tube in a dose of 1 mg. Five animals acted as the control. The animals were killed on the seventh day. Pieces of the renal medulla (papilla) were fixed in 5% glutaraldehyde solution in phosphate buffer (pH 7.4, 0.3 M) and postfixed in 1% osmic acid. The fixed pieces were embedded in a mixture of Epon and Araldite. Ultrathin sections were stained with lead nitrate and examined in the JEM-100B electron microscope under a magnification of 4500. For each animal 50 interstitial cells were investigated and the number of lipid granules in them was counted on developed photographic plates.

EXPERIMENTAL RESULTS

Experimental animals which in their external appearance and behavior were indistinguishable from the controls (10 rats) were used for comparative analysis. The kidneys of the experimental animals were externally of the usual appearance. On sectioning only slight anemia of the medulla and congestion of the cortex were observed. The interstitial cells of the medulla of all the experimental animals contained numerous osmiophilic lipid granules, often four to five times more than in the control. The number of lipid granules in the cells varied from a minimum of nine to ten to 35-40 granules per cell. The mean number of granules was 13.6 ± 1.08. The number of lipid granules in the medullary cells of the control group of animals in most cases was three to five per cell (mean 4.4 ± 0.96). The difference from the control was highly significant ($P < 0.001$).

Granules in the experimental group, just as in the control, varied in size but they were mainly large, densely stained, and osmiophilic (Fig. 1). No granules whatsoever were found with a pale, indistinct periphery. The granules were just as numerous in the perinuclear zone as in the cytoplasmic processes.

Hardly any interstitial cells with no granules, resembling the so-called dark cells which, on the basis of previous investigations, were regarded as the most functionally active [4], could be seen in the renal papilla of the experimental animals. As a rule the cells in the experimental group were vacuolated, with considerable widening of the perinuclear spaces and with the formation of vacuoles lined by smooth membranes. The network of the granular endoplasmic reticulum was poorly developed, but numerous ribosomes were present in the cytoplasm itself. The nucleus of these cells was round in shape, with clearly defined smooth outlines, a quite uncharacteristic appearance for interstitial cells under ordinary conditions of function. The nuclear chromatin was arranged as a homogeneous, finely dispersed layer, with no characteristic focal concentrations (Fig. 2).

The state of the medullary interstitial cells after administration of the inhibitor of prostaglandin synthesis thus differed in principle from the changes observed in experimental situations associated with the mobilization of this synthesis (for example, during forced diuresis and sodium excretion). The increase in

the number of lipid granules under these conditions, in the writers' opinion, is definite proof of their participation in the synthetic function of the interstitial cells as reserve depots of chemical precursors of the prostaglandins.

The increase in the number of lipid granules following administration of indomethacin can be explained, first, by inhibition of prostaglandin synthesis and arrest of the dynamic process of hydrolysis of the triglycerides of the granules to precursors, namely arachidonic acid, and second, by an increase in the esterification of unutilized arachindonates and their deposition as triglycerides in granules.

Anggard [5] showed that interstitial cells contain arachidonic acid in a quantity equivalent to the quantity of prostaglandins synthesized in the medulla. Much of the arachidonic acid is in the composition of phospholipids of the microsomal fraction, where high activity of the enzyme known as prostaglandin synthetase and, as its name implies, concerned in prostaglandin synthesis, is also found. Much of the arachidonic acid is present in the composition of nonpolar lipids (triglycerides, cholesterol esters), which mainly form the lipid granules of the interstitial cells. Hydrolysis of the phospholipids and liberation of prostaglandin precursors take place through the action of phospholipase. Even on the basis of the facts described above the relations between prostaglandin synthesis and lipid granules are a complex, multistage process: this accounts for the complexity of assessment of the synthetic function of the interstitial cells in terms of the number of lipid granules in their cytoplasm. The number of lipid granules in the interstitial cells during the action of mobilizing stimuli may vary depending both on the intensity of prostaglandin synthesis and on the rate and intensity of formation of precursors.

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