EFFECT OF CHANGES IN PROSTAGLANDIN SYNTHESIS ON THE RENIN – ANGIOTENSIN SYSTEM

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Activity of the renin–angiotensin system was investigated in experiments on rats in which prostaglandin synthesis was depressed by indomethacin. Administration of indomethacin in doses not changing the blood pressure was accompanied by a marked decrease in plasma renin activity and in the secretory function of the juxtaglomerular apparatus of the kidneys. The number of lipid granules in the interstitial cells increased at the same time, reflecting inhibition of prostaglandin synthesis in the renal medulla. It is concluded that renin synthesis is coupled with prostaglandin synthesis in the kidney.

KEY WORDS: prostaglandins; indomethacin; juxtaglomerular apparatus.

The effect of prostaglandins (PG) on renin synthesis and secretion has been established by injecting them into the renal blood flow [13, 14]. On the other hand, injection of angiotensin into the renal artery led to the removal of PG from the kidney tissue [9, 12]. Injection of PG into persons with a normal or raised blood pressure also increased the plasma renin activity, especially in the presence of salt deficiency [4]. Other evidence of the interconnection between PG and renin in the kidneys is given by the experiments of McGiff et al. [10], who showed that ischemization of the kidney accompanied by an increase in the plasma renin activity causes as increase in the PG concentration in blood flowing from the kidney. In analogous experiments on rabbits clear dynamic interconnection was demonstrated between the concentration of PG-like substances in the kidneys and the renal activity in their cortex [1].

The object of this investigation was to study the effect of changes in prostaglandin synthesis on the activity of the renin–angiotensin system.

EXPERIMENTAL METHOD

Experiments were carried out on 30 male Wistar rats kept on the same water-salt regimen and on a standard diet. In the course of 5 days 20 rats were given indomethacin (5 mg/kg) in 15% gelatin solution by gastric tube.

The blood pressure was measured plethysmographically in the caudal artery at the beginning of the experiments and on the day before sacrifice. Blood samples from the carotid artery were taken from rats anesthetized with pentobarbital immediately before sacrifice to determine the plasma renin activity.

Pieces of renal medulla were fixed in 5% glutaraldehyde solution in 0.3 M phosphate buffer and processed for electron microscopy. Lipid granules of the interstitial cells were investigated in the electron microscope and in semithin Epon sections stained with methylene blue. Lipid granules were counted on developed photographic plates taken with a magnification of 4200 ×.

The plasma renin activity was determined radioimmunologically [11] using the set of reagents prepared by the firm "Ire-Sea-Sorin." Rat plasma taken from the animals 72 h after bilateral nephrectomy was used as the substrate. Renin activity was expressed in nanograms angiotensin I formed in 1 ml plasma during incubation for 1 h at 37°C. To calculate the juxtaglomerular index (JGI) pieces of kidney cortex were fixed in

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Zenker's fluid, embedded in paraffin wax, and sections were stained by Bowie's method [5].

EXPERIMENTAL RESULTS AND DISCUSSION

The blood pressure of the animals receiving indomethacin was virtually the same at the end of the experiments (80 ± 4.9 mm Hg) as initially (85 ± 6.0 mm Hg) or that of the control rats (90 ± 4.5 mm Hg).

The plasma renin activity of the control animals averaged 25.3 ± 3.6 ng/ml/h. The renin activity was significantly lower in the experimental animals, namely 16.4 ±2.5 ng/ml/h, with variations from 2.6 to 36.8 ng/ml/h ($P < 0.05$). Indomethacin led to a marked reduction in the granularity of the epithelioid cells of the afferent artery of the renal glomeruli, with a marked decrease in JGI (9.6 ± 2.35 compared with 61.8 ± 6.74 in the control; $P < 0.001$).

The inhibitor of PG synthesis, by lowering the plasma renin activity in the animals, thus evidently led to inhibition of PG synthesis in the juxtaglomerular apparatus of the kidneys also.

The interstitial cells of the renal medulla in the experimental animals contained far more lipid granules than in the control (10.7 ± 1.25 compared with 3.38 ± 0.5 in the control; $P < 0.001$) and a well developed smooth endoplasmic reticulum. Optically dark cells filled with free and fixed ribosomes were almost completely absent in these animals. Such cells are frequently found in experimental situations connected with the activation of PG synthesis (for example, after administration of substances promoting sodium excretion [2]); in the writers' view they are functionally active. These observations point to inhibition of the synthesis of renal PG in the experimental animals. In the modern view, the PG precursor arachidonic acid is formed in the lipid granules of the interstitial cells. Inhibition of PG synthesis may be accompanied by an increase in the number of lipid granules as a result of increased esterification of the unused fatty acids and their deposition in the form of triglycerides. The number of granules may also increase as the result of the blocking of lipolysis during inhibition of PG synthesis. These observations agree with the results of experiments on rabbits which showed that administration of indomethacin considerably reduces the PG content in kidney tissue and increases the number of lipid granules in the interstitial cells of the medulla [3].

Inhibition of synthesis of renal PG is evidently the cause of the depression of the synthesis and secretion of renin, for specific activation of PG synthesis (by injection of arachidonic acid) is accompanied by increased plasma renin activity [8]. The writers showed previously [2] that if a functional load is thrown on the kidney (by administration of substances promoting sodium excretion or by restricting fluid) the decrease in the number of lipid granules in the medullary interstitial cells, indicating increased PG synthesis, is accompanied by increased renin activity.

The most likely factor linking PG synthesis with the function of the juxtaglomerular apparatus of the kidneys is a change in the renal hemodynamics. Experiments on the perfused dog kidney have shown that PG acts on the juxtamedullary blood flow, which is reduced if their synthesis is inhibited [6]. On the other hand, stimulation of the synthesis of renal PG leads to an increase in the juxtamedullary blood flow [7]. The accompanying zonal redistribution of the blood flow in the kidneys may act on the function of the juxtaglomerular apparatus. Other mechanisms whereby the renal PG exert their influence on the renin–angiotensin system of the kidneys may also exist. Stimulation of sodium excretion by PG may alter the sodium concentration at the level of the "dark spot" in the distal tubule, which acts directly on the juxtaglomerular apparatus. PG may also have a direct action on renin-forming cells.

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