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Stimulation of Renin Release by Prostaglandin E_2

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The effect of different doses of prostaglandin E_2 on renin secretion in isolated perfused rat kidney has been studied. The infusion of 5 ng/ml of prostaglandin E_2 produced a significant rise on renin secretion compared with control group. A dosage increase of prostaglandin E_2 (10 and 50 ng/ml) produced an increase in the released renin. From this a correlation between doses and responses can be obtained.

The perfusion pressure was slightly — but significantly — modified wiht the highest doses of prostaglandin (50 ng/ml). The possible pathways of action are dicussed.

The antihypertensive role of kidney postulated by GOLDBLAT in 1934 (5) has been now ascribed to its content on prostaglandin (6-8). However, STRONG *et al.* (14) and EWARDS *et al.* (3) have reported a marked increase in renin and prostaglandin on some patients with renovascular hypertension.

Although recently has been postulated a direct effect of prostaglandin on renin secretion and activity *in vitro* (4, 10, 19); these results were not in accordance with previous reports (1, 15).

The present work was designed to study the effect of prostaglandin E_2 (PGE_2) on renin secretion using the isolated perfused kidney of the rat.

Materials and Methods

Perfusion fluid was Krebs-Ringer saline pH 7.4 with 3.6 % dextran (m.w. 70.000) bubbled with 95 % O_2 and 5 % CO_2. The prostaglandin E_2 was dissolved in Krebs with a final ethanol concentration of 5 $^0/_{00}$

Kidney perfusion. Male Wistar rats (300 g) were anaesthetized with sodium pentobarbitone (0,1 mg/g) and heparinized intravenously (100 U). The left kidney was isolated and perfused without inter-

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ruption of blood flow as previously has been described (16). The perfusion flow was usually 8 ml/min and perfusion pressure was monitored by transducer and Devices M-2 recorder. The first sample was collected after 5-7 minutes, when mean renal perfusion pressure had stabilized. Samples were also collected 10, 20 and 30 minutes from first sample. The prostaglandin were administered for 20 minutes.

Renin assay. Perfusion samples were dialysed successively to pH 4.5 (24 hours) and pH 7.5 (24 hours) at 4° C against phosphate buffers containing EDTA-(Na_2) to remove angiotensinases (13).

Samples were then incubated at 37° C with nephrectomized rat plasma as substrate which was also treated by the method of Skinner. The enzymatic reaction was stopped by heating the samples to 85-90° C for 10 minutes. The incubation product (Angiotensin I) was measured by radioimmunoassay and renin concentration expressed as ng equivalent of Ileu^5-Angiotensin I generated per ml of perfusing per hour incubation.

To avoid the biological variability on basal renin concentration among different groups of rats, the results were referred as the ratio:

$$\Delta \text{ Renin concentration} = \frac{\text{Renin concentration tn}}{\text{Renin concentration to}}$$

wehere: tn = timed samples (n = 10, 20 and 30 minutes from to); to = first sample.

All results are expressed as mean ± s.e.m. The statistical analysis of data was made by the paired Student's «t» test.

Results

The effect of PGE_2 on renin production is shown in figure 1. An increase significant over control group ($p < 0.001$) was seen at 5 ng/ml/min, and at 10 and 50 ng/ml/min, the stimulation on renin release was also significant ($p < 0.001$). In all cases the dynamics of secretion show a similar pattern and the peak in renin production was reached 20 minutes from the start.

Figure 2 shows a dose response linearization, obtained when the maximal increase in renin (20 minutes from the start) was compared with the logarithm of different doses used in this study.

Table I, summarizes the data of perfusion pressure in the different experiments. The control group had a stabilized pressure at 60 mm Hg. The prostaglandin at 5 ng/ml/min ($p > 0.5$) and 10 ng/ml/min ($p > 0.1$) did not produce any significant change on perfusion pressure. The dose of 50 ng/ml/min produced a significant rise ($p < 0.05$) on pressure compared with the control group.

Neither propranolol (0.9 μg/min) nor phenoxybenzamine (0.7 μg/ml/min) prevented the pressure rise caused by PGE_2 50 ng/ml/min.

Discussion

It has been shown that prostaglandin E_2 produces a significant increase in renin secretion in the isolated perfused rat kidney (fig. 1). This effect is in accordance with previous works showing a stimulating action on renin release by PGE_1 in dog (19) and prostaglandin A_1 in man (4, 10).

The stimulating effect of PGE_2 on renin secretion seems to be specific as it is demonstrated by the positive correlation between doses of prostaglandin infused and the renin released (fig 1); therefore, when the logarithm of doses was plotted against the renin produced, a straigth line was obtained (fig. 2).

Despite this effect it is difficult to find the possible pathway of PGE_2 action on renin secretion. Three possibilities could be discused: *a*) an increase in activity of

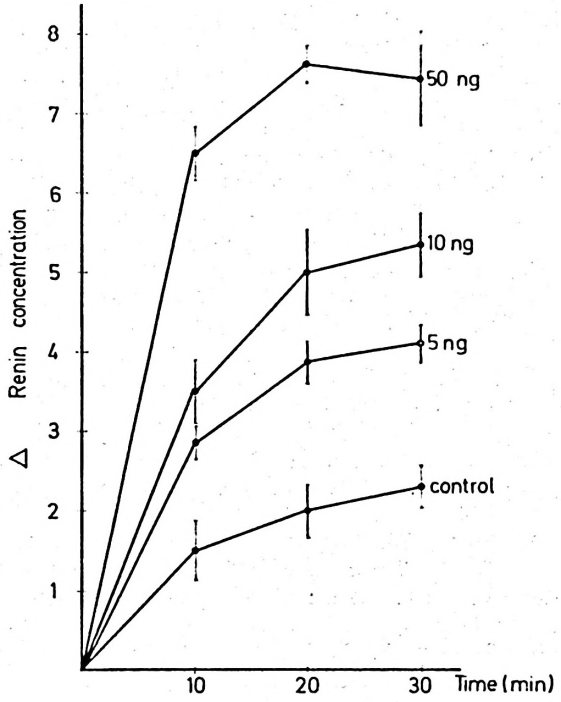

Fig. 1. *Effect of different doses of prostaglandin E_2 on renin secretion (mean±s.e.m.) in the isolated perfused rat kidney.*

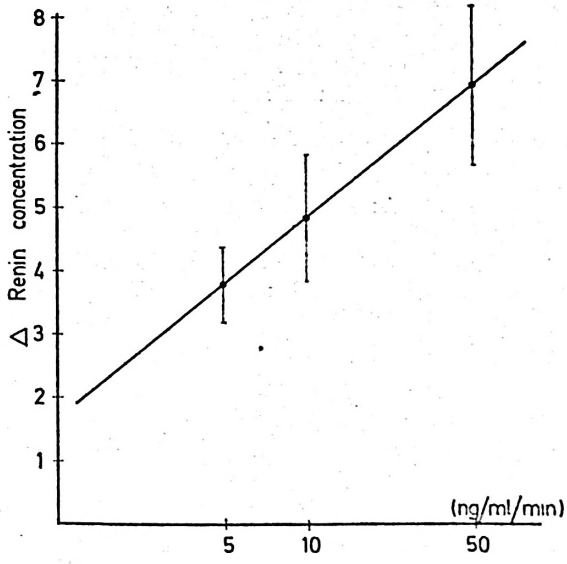

Fig. 2. *Correlation betwen the logarithm of prostaglandin E_2 doses infused (abscissae) plotted against the peak in renin secretion (20 minutes from start) (ordinates).*

Table I. *Effect of different doses of prostaglandin E_2 on perfusion pressure (mm of Hg) in control group and with different doses of prostaglandin.*

In parenthesis number of experiments per group. Mean ± s.e.m. For significances see text.

PGE_2 (ng/ml)	Time (minutes) 10	20	30
(17)	60.00±2.0	61.25±3.5	60.20± 2.8
5 (9)	60.00±1.7	61.00±2.9	62.00± 3.5
10 (8)	60.25±6.2	68.75±4.8	78.75± 4.8
50 (6)	80.00±5.1	82.60±7.3	85.10±10.5

adenyl cyclase system, *b*) a reduced tubular sodium reabsorption rate or, *c*) change in the intracellular levels of calcium.

The prostaglandin increases the activity of adenyl cyclase system leading to the increase in 3′-5′-cyclic adenosine monophosphoric acid (cAMP) (20) and different authors have proposed that a rise in cAMP levels could cause a stimulation on renin secretion (11, 18). However, it has been reported in the isolated perfused rat kidney, that neither cyclic AMP nor dibutyryl cyclic AMP produced a stimulating effect on renin release (12).

The PGE_2 increases sodium excretion by an inhibition of tubular reabsorption; this decrease of sodium reabsorption could cause the release of renin by kidney (2). However, the diuretic effect of PGE_2 is not immediate (2) and increase on renin secretion is obtained immediately after infusion of PGE_2 (fig. 1); therefore, it is difficult to accept this mechanism to explain the effect on renin production.

Recently, it has been proposed the important role of calcium on the mechanism of renin secretion. Vasoconstrictor substances like angiotensin and antidiuretic hormone, increasing the intracellular calcium concentration could inhibit the release of renin by juxtaglomerular cells (17). If prostaglandin caused vasodilation (9) a decrease in intracellular calcium concentration can be assumed and relate

this change to renin stimulation. However, from the present results the highest PGE_2 concentration (50 ng/ml) caused an increase in perfusion-pressure accompanied by a stimulation on renin secretion (table I).

Resumen

Se ha estudiado, en riñón aislado y perfundido de rata, el efecto de diversas dosis de prostaglandina E_2 sobre la secreción de renina. En comparación al grupo control, la infusión de 5 ng/ml de prostaglandina E_2 causa un aumento significativo de la secreción de renina, demostrándose que aumentando las dosis a 10 y 50 ng/ml existe una clara relación entre dosis y respuesta. La presión de perfusión se modificó leve, aunque significativamente, con la dosis mayor de prostaglandina (50 ng/ml). Se discuten sus posibles mecanismos de acción sobre la secreción de renina.

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