Effects of prostaglandins on renin substrate production by the liver

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Summary
1. The effects of prostaglandin (PG) E₁, PGE₂ and PGF₂α on plasma renin substrate concentration in rats and renin substrate production by perfused rat liver were investigated.
2. After bilateral nephrectomy, both plasma renin substrate concentration and renin substrate production were remarkably elevated.
3. The increase in plasma renin substrate level and production of renin substrate by the liver after nephrectomy was markedly suppressed by the treatment with PGE₁ or PGE₂.
4. In contrast PGF₂α had no suppressive effect on renin substrate synthesis.
5. These findings suggest that PGE₁ and PGE₂ might be inhibitory factors in the regulation of renin substrate synthesis.

Key words: angiotensin, liver perfusion, nephrectomy, prostaglandins, renin substrate.

Introduction
The inter-relation between renin–angiotensin and kallikrein–kinin systems is of great current interest and prostaglandins are considered to play an important role as intermediates (Levinsky, 1979). Although prostaglandins participate in the release of renin (Oates, Whorton, Gerkens, Branch, Hollifield & Fröhlich, 1979), there has been no report concerning the effects of prostaglandins on renin substrate production.

This study aims to demonstrate the effects of prostaglandin (PG) E₁, PGE₂ and PGF₂α on renin substrate production by the perfused rat liver in normal and nephrectomized rats. The effects of these PG species on plasma renin substrate concentration were also studied in nephrectomized rats.

Materials and methods
Female Wistar rats (250–300 g) were used. The isolated rat liver perfusion was performed to study renin substrate formation. The details of the liver-perfusion procedure have been described previously (Murakami, Hiwada & Kokubu, 1980).

Liver perfusion was carried out in the following groups of animals: (1) normal rats; (2) rats bilaterally nephrectomized 24 h previously; (3) nephrectomized rats to which 25 pg of PGE₂ or of PGF₂α was intraperitoneally administered every 6 h (total 100 pg); (4) normal rats with 100 µg each of PGE₁, PGE₂ or PGF₂α continuously added to the perfusate with a peristaltic pump during the first h of liver perfusion; (5) nephrectomized rats given PGE₁, PGE₂ or PGF₂α (1–250 µg) intraperitoneally 2 h before the perfusion [the same dose of PG (1–250 µg) was continuously infused during 1 h of perfusion].

The liver perfusion lasted for 2 h and samples (2 ml) were removed from the perfusate at 0, 1 and 2 h after the start of perfusion. Renin substrate content of the perfusate was assayed by the method reported previously (Murakami et al., 1980). The doses of PG used in the present study did not affect the reaction of renin substrate in the perfusate with renin in vitro. The production rate of renin substrate by the perfused liver was expressed as ng of angiotensin I (ANG I) equivalent/g of liver in 2 h.

In groups (1), (2) and (3), plasma renin substrate concentration was measured by radioimmunoassay for ANG I as reported previously (Hiwada, Tanaka, Murakami, Ono & Kokubu, 1979).
Statistical analysis was performed by Student's t-test. Values are given as mean ± SEM.

Results
The amount of renin substrate produced by normal rat liver increased linearly during 2 h of perfusion and was 55.9 ± 4.5 ng of ANG I equivalent/g of liver in 2 h (n = 8).

After nephrectomy, the level of plasma renin substrate concentration was remarkably elevated, averaging 5070 ± 745 ng of ANG I equivalent/ml (n = 6) compared with 392 ± 42 ng of ANG I equivalent/ml (n = 6) in normal rats (P < 0.001). Plasma renin substrate concentration in nephrectomized rats was significantly reduced to 3615 ± 238 ng of ANG I equivalent/ml (n = 8) by the intraperitoneal injection of PGE₂ (100 μg) (P < 0.001).

The amount of renin substrate produced by the livers of nephrectomized rats with intraperitoneal administration of PGE₂ was 212.7 ± 14.0 ng of ANG I equivalent/g liver in 2 h, which was also significantly decreased to a half of that from nephrectomized rats (P < 0.001).

PGF₂α had no suppressive effects either on renin substrate synthesis or on plasma renin substrate concentration.

When PGE₁ or PGE₂ (100 μg) was added to the perfusion of normal rat liver, the production of renin substrate significantly decreased, to 30.7 ± 4.2 and 29.4 ± 2.7 ng of ANG I equivalent/g of liver in 2 h (n = 5) respectively (P < 0.005). PGF₂α (100 μg) did not affect the synthesis of renin substrate.

The increase of renin substrate production after nephrectomy was significantly suppressed by addition of PGE₁ or PGE₂ in doses greater than 20 μg and the maximum effect of suppression could be observed when more than 200 μg of PGE₁ or PGE₂ was added. The amount of renin substrate in the perfusate was approximately one-third of that for nephrectomized rats (P < 0.001). PGF₂α (200 μg) had no suppressive effect on renin substrate production in nephrectomized rats.

Discussion
The regulatory mechanism for renin substrate synthesis by the liver remains to be established. The perfused liver is a good model for studying the modulation of renin substrate production. There are parallels between renin–angiotensin and kallikrein–kinin systems, such as renin substrate and kininogen. Recently, PGE₂, but not PGF₂α, has been shown to produce a significant decrease in plasma kininogen (Sharma, 1978).
Our present study showed that PGE₁ or PGE₂ could decrease the synthesis of renin substrate and the plasma renin substrate concentration, but PGF₂α had no such effects.

After nephrectomy, a marked increase of renin substrate production by the isolated liver was observed. Therefore, a remarkable elevation in plasma renin substrate concentration after nephrectomy could be explained by an increased rate of renin substrate formation rather than a decreased consumption by renin. From this study and our previous data (Hiwada, Tanaka & Kokubu, 1976), it can be postulated that the kidney produces inhibitory factors for the synthesis of renin substrate by the liver.

PGE₂ is synthesized in the kidney and is released into the renal vein (Dunn, Liard & Dray, 1978). The extraction of PGE₂ in the lung is about 96% during pulmonary circulation (Gerkens, Friesinger, Branch, Shand & Gerber, 1978). Thus it is possible that a small proportion of PGE₂ synthesized in the kidney passes through the lung and can act as a circulating hormone. Our observation that a pronounced increase in plasma renin substrate concentration and renin substrate production after nephrectomy is markedly suppressed by administration of PGE₂ suggests that PGE₂ might be one of the inhibitory factors originating in the kidney which regulates renin substrate synthesis by the liver.

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References


