Angiotensin blockade in studies of the feedback control of renin release in rats and rabbits

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Summary

1. In rabbits actively immunized against angiotensin II (All), the appearance of anti-A11 antibodies was associated with a rise in plasma renin activity (PRA), which did not occur in mock-immunized controls.

2. In conscious rabbits, infusion of the angiotensin inhibitor, Sar"-Ala"-angiotensin II (P-113), at rates of 0.055, 0.22 or 1.1 nmol min⁻¹ kg⁻¹ into the renal artery, caused dose-related increases in arterial PRA and renal arteriovenous PRA difference. Renal blood flow fell with the high dose, but not with the low or medium doses. A fall in arterial pressure, asynchronous with peak renin secretion, accompanied the medium- and high-dose infusions.

3. Intravenous infusion of inhibitor P-113, 5.5 nmol min⁻¹ kg⁻¹, into anaesthetized rats produced highly significant increases in PRA and plasma renin concentration without reduction in arterial pressure. There were no changes in PRA or plasma renin concentration in saline-infused control rats.

4. These findings suggest that A11 blockade interrupts a negative feedback loop controlling renin secretion.

Key words: angiotensin II, angiotensin antibodies, inhibitor P-113, plasma renin.

Introduction

Based on the finding that pharmacological elevation of circulating angiotensin II (AII) levels reduces renin release, it has been proposed that renin secretion is controlled by a negative feedback system (Vander, 1967). If this system is of physiological importance, lowering the circulating level of endogenous angiotensin should produce a reciprocal increase in renin secretion. Evidence for such a response has been obtained in rats (Bing, 1973) and renal hypertensive dogs (Miller, Samuels, Haber & Barger, 1972) treated with angiotensin-converting enzyme inhibitor. The aim of the present experiments was to determine whether interruption of the negative feedback loop by active immunization against AII or by intravenous or intrarenal infusion of the competitive inhibitor, Sar"-Ala"-angiotensin II, would also lead to increased renin release.

Materials and methods

Experiments were performed in New Zealand white rabbits (2.5-4.0 kg) and adult Wistar rats (480-530 g) allowed free access to a standard pellet diet and tap water.

Group I. Six rabbits were immunized against AII as described by Oates & Stokes (1974). Five rabbits were mock-immunized. Each week 1 ml of blood was taken for measuring plasma renin activity and antibodies against AII.

Group II. In eleven male rabbits, 3 weeks after right nephrectomy and 2 days after catheterization of the left renal blood vessels, catheters were inserted into the central ear vessels and bladder, under local anaesthesia. Arterial blood pressure and renal plasma flow (p-aminohippurate clearance/renal extraction ratio) were then measured with the animal sitting in a box (Stokes & Korner, 1964). Arterial and renal vein blood samples, totalling 15 ml in 3 h, were replaced serially by a protein–saline solution (Weber, Thornell & Stokes, 1973). Arterial pressure, renal blood flow and plasma renin activity were
Plasma renin activity, plasma renin concentration and angiotensin antibody titres were measured by radioimmunoassay (Oates & Stokes, 1974).

Results

Group I

Mean PRA\((1)\) during a 6 weeks pre-immunization period was 17·4 ± 1·3 (SEM) ng h\(^{-1}\) ml\(^{-1}\). During the first week that antibody against AII was detected (mean titre 1/10 000), PRA increased \((P<0·02)\) to 263\(\%\), reaching 45·7 ± 10·7. It then fell despite progressive increases in anti-AII antibody titres. Mean PRA after mock-immunization was not significantly different from the control rabbit values.

Group II

The effects of 1 h infusions of inhibitor P-113 into

\((1)\) Abbreviations: PRA, plasma renin activity; AII, angiotensin II; a-v, arteriovenous.
the renal arteries of one-kidney conscious rabbits are shown in Fig. 1. During the control period, the renal arteriovenous (a-v) PRA difference indicated net renin secretion in each animal. Mean control arterial PRA was 17.9 ± 4.0 (SEM) ng h⁻¹ ml⁻¹ (n = 11) and mean control renal vein PRA was 24.9. During and after infusion of inhibitor P-113 at 0.055 nmol min⁻¹ kg⁻¹ in two animals there were no changes in mean arterial pressure or renal blood flow. Arterial pressure rose slightly during the infusion. Within 50 min of starting infusion of inhibitor P-113 at 0.22 nmol min⁻¹ kg⁻¹ (n = 6), mean arterial pressure fell by 9.7 mmHg (P < 0.05) and mean arterial PRA rose to 267% of the control value (P < 0.05). Renal a-v PRA difference reached a mean value of 348% of control (P < 0.01) at 30 min and then fell. Mean renal blood flow did not change (n = 4). Infusion of inhibitor P-113, 1.1 nmol min⁻¹ kg⁻¹, produced falls in arterial pressure (mean 14 mmHg) and renal blood flow in all three animals tested. Changes in arterial PRA and renal a-v PRA difference paralleled those obtained with infusion of 0.22 nmol min⁻¹ kg⁻¹ inhibitor, but were greater in magnitude. During the 1 h period after infusion of the medium and high doses of inhibitor P-113, the measured variables reverted to their pre-infusion values in most animals.

Groups IIIa and IIIb

Mean values for PRA and plasma renin concentration in the three serial pre-infusion samples were constant within both groups of rats (range: PRA 2.0–2.3; plasma renin concentration 70.1–78.1 ng h⁻¹ ml⁻¹). They remained constant for 1.5 h after the infusion of saline for 1 h (group IIIb). However, infusion of inhibitor P-113 for 1 h (group IIIa) resulted in a steep rise in PRA to 652% of control value (P < 0.001) and in plasma renin concentration to 724% (P < 0.001). Thirty minutes after stopping the infusion, PRA had fallen to 300% and plasma renin concentration to 278% of pre-infusion values, but even after 1.5 h a small but insignificant difference in mean values remained between group IIIa and group IIIb.

Immediately after starting infusion of inhibitor P-113, blood pressure rose transiently by 8 mmHg. A similar rise occurred on stopping the infusion. At no stage, however, were the mean values for pressure or heart rate of group IIIa rats significantly different from those of group IIIb.

Discussion

Previous studies in sodium-depleted or caval-constricted dogs (Johnson & Davis, 1973) and in adrenalectomized rats (Bing, 1973) have shown that PRA increases during infusion of inhibitor P-113. However, these studies, in which arterial pressure, where reported, was reduced, have not established whether the rise in PRA was produced by interruption of AII-mediated feedback control of renin release or by baroreceptor stimulation. The present experiments have established that inhibitor P-113, 5-5 nmol min⁻¹ kg⁻¹, increases PRA and plasma renin concentration in ganglion-blocked, vagotomized rats without significant effects upon their arterial pressure or heart rate.

In conscious rabbits, infusion of inhibitor P-113, 0.22 nmol min⁻¹ kg⁻¹, into the renal artery caused rises in arterial PRA and renal a-v PRA difference without change in renal blood flow, constituting direct evidence of increased renin secretion. It seems unlikely that this was secondary to hypotension, for the peak response in renin secretion preceded the lowest arterial pressure. Also, a four-fold rise in renin secretion was observed in one rabbit despite a definite increase in its arterial pressure during infusion of inhibitor P-113. The asynchrony between the peak renin response and the cessation of infusion of inhibitor P-113 is consistent with initial interruption of the AII feedback loop, followed by breakthrough of the blockade by rising arterial AII concentrations.

The rise in PRA in AII-immunized rabbits suggests that renin release also increases when the concentration of free circulating AII is reduced, again consistent with the properties of a negative feedback system. The secondary fall in PRA observed in this group has been discussed (Oates & Stokes, 1974).

References


