Intrarenal control of urine concentration by angiotensin II

J. L. IMBS, M. SCHMIDT and J. SCHWARTZ
Service d’Hypertension artérielle et Institut de Pharmacologie, Faculté de Médecine, Strasbourg, France

Summary
1. The intrarenal role of angiotensin II in the recovery of urinary concentration after frusemide was examined in anaesthetized dogs by the intrarenal infusion of angiotensin II antagonists.
2. Renin secretion and renal inner medullary blood flow (tissue clearance of intraparenchymatously injected $^{133}$Xenon) were simultaneously measured before and 3 h after frusemide injection.
3. Intrarenal angiotensin II blockade delayed the recovery of urinary osmolality after frusemide.
4. An inverse relationship was found between renin secretion and renal inner medullary blood flow.

Key words: angiotensin II antagonists, renal medullary blood flow, renin release, urine concentration.

Introduction
The urinary concentration which follows dehydration is accompanied by an increase in the release of angiotensin. The use of antagonists has made possible the demonstration that under such conditions, angiotensin II contributes to sodium retention through its endorenal effect (Hall, Guyton, Trippodo, Lohmeier, McCaa & Cowley, 1977). We therefore studied the role of angiotensin in maintaining the cortico-papillary concentration gradient, which in the presence of vasopressin, allows the osmotic reabsorption of filtered water.

In this study we exploited the properties of frusemide which reduces the cortico-papillary concentration gradient. Since its effect is short-lived, it is possible to follow the reappearance of the urinary concentration mechanism within a few hours. Frusemide produces renin hypersecretion which can be inhibited by propranolol, an effect which has been shown to delay the reappearance of the urinary concentration mechanism when the effect of the diuretic has worn off. In the anaesthetized dog, urinary osmolality remains low much longer (Imbs, Schmidt, Velly & Schwartz, 1977), and in the conscious rat, the recovery of the cortico-papillary gradient for sodium is slowed down (Imbs, Schmidt & Schwartz, 1976). These results led us to study the role of angiotensin in the control of renal medullary blood flow. The intrarenal concentration gradient is maintained by the countercurrent exchange mechanism brought about by the vasa recta in the renal medulla. This countercurrent exchange is only effective in the presence of a low blood flow in the vasa recta. By a constrictive action on the efferent arterioles of the juxtamedullary glomeruli from which the vasa recta originate, angiotensin can ensure this necessary condition for urinary concentration.

In the dog treated with frusemide, we first verified whether angiotensin II antagonists reproduced the effect of inhibiting renin secretion on urinary osmolality. In a second series of experiments, we measured local blood flow in the inner renal medulla during frusemide-induced variations in renin secretion.

Materials and Methods

General procedure
Twenty dogs of either sex, weighing 15–25 kg, were anaesthetized with pentobarbital (35–45 mg/kg). Appropriate blood vessels were catheterized for intravenous injection and blood
pressure. The left kidney, exposed by a retroperitoneal flank incision, was denervated and its lymphatics ligated. An electromagnetic flow probe was placed around the renal artery to measure blood flow. The ureter was cut and catheterized. Throughout the experiment the kidney remained outside the abdominal cavity and covered with gauze kept moist with saline. Measurements began 1.5 h after surgery.

Intrarenal infusion of angiotensin II antagonists in frusemide-treated dogs

In 14 dogs, a curved needle was inserted into the left renal artery. Each animal was given an intravenous injection of frusemide (60.6 µmol/kg; 20 mg/kg). In five dogs, an intrarenal infusion of an angiotensin II competitive antagonist was started 15 min before the injection of diuretic and continued for 6 h. Two of these 5 dogs received 1.03 µmol min⁻¹ kg⁻¹ (1 ng min⁻¹ kg⁻¹) of (1-sarcosyl-5-valine-8-alanine) angiotensin II (saralasin); the other three received 0.94 µmol min⁻¹ kg⁻¹ (1 ng min⁻¹ kg⁻¹) of (1-succinamoyl-5-valine-8-phenylglycine) angiotensin II (Hoe 409). At the end of the experiment, we checked that these doses of antagonists completely inhibited the renal response to an intrarenal injection of 24 µmol/kg (25 ng/kg) of valine-5-angiotensin II (Hypertensin). Nine control animals received an intrarenal infusion of saline. All the intrarenal infusions were given at a rate of 0.1 ml/min. Urine was collected in several fractions: the first during the 15 min preceding the frusemide injection, the remaining six at hourly intervals after this injection. Volume, osmolality (cryometry) and sodium excretion (flame photometry) were measured for each urine sample.

Renal inner medullary blood flow measurements

Local blood flow was measured in 6 dogs with the ¹³³Xe tissue clearance method. A solution of ¹³³Xe (300–400 µCi in 0.25 ml of saline) was injected into the renal medulla using thread-like glass needles (external diameter: 150µm) inserted into the left kidney. During blood flow measurement, urine was collected in a flexible plastic container placed under the kidney, in the field of a scintillation detector (3 inch sodium iodide crystal). Under these conditions, the radioactivity decay curve for the whole kidney-urine reservoir was due only to the washout of the ¹³³Xe by the blood flow. Only those measurements in which the radioactivity decay curve followed a monoexponential curve were used in calculating local blood flow (Ladefoged, Pedersen, Douthell, Deetjen & Selkurkt, 1965). At the end of the experiment, the kidney was removed, care being taken to leave the glass needles in place. The point where xenon had been injected was located in the inner or outer medulla by dissection under a microscope.

Two successive measurements of local blood flow were made: the first before administering the diuretic; the second, 3 h after the intravenous injection of frusemide. Renin secretion was also measured at the same time. Plasma renin activity was determined by radioimmunoassay (Haber, Koerner, Page, Kliman & Purnode, 1969). Renin secretion rate was calculated as (renal venous plasma renin activity – systemic arterial plasma renin activity) × renal plasma flow. Glomerular filtration rate was measured by polyfructosan clearance.

Results

Intrarenal infusion of angiotensin II antagonists did not affect either blood pressure or renal blood flow after frusemide. No agonistic effects of the angiotensin II analogues appeared to occur. Following the fourth hour after the diuretic injection, urinary osmolality failed to increase in the angiotensin II antagonist treated group (Fig. 1). Six hours after the diuretic injection, osmolality was only 352 mosmol/kg (SEM 22, n = 5) in this group, compared with 460 mosmol/kg (SEM 88, n = 9, P < 0.025, Student's t-test) in the control group.

In the 6 dogs in which inner medullary blood flow measurements were made, we found an increase in renin secretion after frusemide injection (2.7 ± 0.68 SEM, n = 19, compared with 0.9 ± 0.53 SEM, n = 19, ng of angiotensin I equivalent min⁻¹ g⁻¹ of kidney, P < 0.025, Student's t-test on matched pairs). Inner medullary blood flow tended to be lower (8.2 ± 0.6 SEM, n = 19, compared with 12.5 ± 1.15 SEM, n = 19, ml 100 g of tissue⁻¹ min⁻¹, P < 0.10). There was an inverse correlation between inner medullary blood flow on one hand and on the other, renin secretion and arteriovenous plasma renin activity difference (r = -0.492, n = 38, P < 0.01, stepwise regression analysis). However, there was no significant correlation between inner medullary blood flow and glomerular filtration rate (r = 0.077, n = 38) or total renal blood flow (r = 0.286, n = 38).
Angiotensin and control of urine concentration

Fig. 1. Evolution of mean arterial pressure and renal function during the 6 h after frusemide injection (at time zero) in dogs receiving intrarenal infusion of angiotensin II antagonists (broken line, \( n = 5 \)) or saline (continuous line, \( n = 9 \)). Values are mean results ± SEM; **\( P < 0.02 \) (Student’s t-test).

Discussion

The results show that in frusemide-treated dogs, intrarenal infusion of angiotensin II antagonists delays the recovery of urinary osmolality, thus reproducing the results obtained by inhibiting renin secretion with propranolol. We observed an inverse correlation between inner medullary blood flow and renin release. These results are consistent with the hypothesis that vasa recta blood flow is controlled by a constrictive effect of angiotensin on the efferent arteriole of the glomerulus. The use of \(^{133}\)Xenon tissue clearance to measure renal medullary blood flow is controversial (Aukland, 1976). Our method allows for the passage of the isotope into the urine; the localized xenon injection within a homogeneous kidney zone gives a mono-exponential rather than a multiexponential radioactivity decay as is the case with an intra-arterial renal injection. The method might, however, be affected by the possibility that xenon follows the countercurrent multiplier system. If this mechanism were important, the reduction of the intrarenal concentration gradient by frusemide should increase the rate of disappearance of the isotope injected into the renal medulla. The results in fact show the contrary.

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References


