SHORT COMMUNICATION

Intrarenal role of angiotensin II in controlling sodium excretion during dehydration in dogs

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Summary

1. The intrarenal role of angiotensin II in controlling sodium excretion was examined in anaesthetized, dehydrated dogs by infusing the angiotensin II antagonist Sar¹-Ile⁸-angiotensin II directly into the renal artery. Comparisons were made with dehydrated dogs receiving only sodium chloride solution intrarenally.

2. Intrarenal angiotensin II blockade resulted in significant increases in urinary sodium excretion and urine flow rate.

3. The results indicate that during the high-renin state of dehydration endogenous angiotensin II has intrarenal effects which lead to salt and water retention.

Key words: angiotensin II antagonist, electrolyte excretion, glomerular filtration rate, renal blood flow.

Introduction

Studies with angiotensin II antagonists have consistently shown an important role of endogenous angiotensin II in the regulation of renal blood flow during high-renin states such as sodium depletion; however, conflict persists as to the intrarenal role of angiotensin II in controlling urinary sodium excretion. Some investigators have found no consistent change in urinary sodium excretion when the competitive antagonist Sar¹-Ala⁸-angiotensin II was infused directly into the renal artery of dogs having high plasma renin activity due to experimental heart failure, vena caval constriction or sodium depletion (Freeman, Davis, Vitale & Johnson, 1973; Freeman, Davis, Spielman & Lohmeier, 1975). Conversely, others found significant increases in urinary sodium excretion in sodium-depleted dogs after intrarenal infusion of the converting enzyme inhibitor SQ 20881 (Gagnon, Rice & Flambaum, 1974; Kimbrough, Vaughan, Carey & Ayers, 1975). In sodium-depleted rabbits, neither the angiotensin II antagonist nor the converting enzyme inhibitor produced an increase in urinary sodium excretion when infused intravenously (Mimran, Guiod & Hollenberg, 1974).

Possible reasons for the inconsistent effects of the blocking agents of the renin-angiotensin system on sodium excretion are: (1) the use of different types of blocking agents (unlike the competitive antagonists of angiotensin II, converting enzyme inhibitor potentiates the action of bradykinin, which is a natriuretic agent); (2) variable falls in mean arterial pressure during blockade of the renin-angiotensin system may cause various degrees of antinatriuresis; (3) changes in the rate of sodium excretion during the experimental period due to undefined responses of the experimental animal to prolonged anaesthesia, surgery and other altered physiological variables.

In this study we have examined the effect of intrarenal infusion of the angiotensin II antagonist Sar¹-Ile⁸-angiotensin II on urinary
sodium excretion and other renal functions in dehydrated dogs, where plasma renin activity was high. The doses and antagonist used were chosen to eliminate the problems of bradykinin potentiation and arterial pressure lowering. To assess the role of anaesthesia and surgery in the experimental results, control studies were made in a group of dehydrated dogs not receiving the antagonist.

Methods

Eleven dogs of either sex, weighing 15-25 kg and maintained on standard dry dog food (12% water content) ad libitum, were dehydrated by water deprivation for 4 days. Subsequently, the dogs were anaesthetized with sodium pentobarbital (30 mg/kg). Appropriate blood vessels were catheterized for intravenous infusion and arterial pressure recording.

Through a retroperitoneal flank incision catheters were placed in the left renal vein (via the gonadal vein) and left ureter, and a non-cannulating electromagnetic flow probe was placed on the left renal artery for measuring renal blood flow. Flow probes were previously calibrated with a stop watch and graduated cylinder with dog blood flowing through transected renal arteries in situ or carotid arteries in vitro. Zero flow was checked by occluding the renal artery after each experiment. A curved 23 gauge needle was inserted into the left renal artery, and an infusion of sodium chloride solution (154 mmol/l; saline) was begun at 0.11 ml/min.

At 1-2 h after surgery, arterial blood was collected for analysis of plasma renin activity and electrolytes. The effects on renal function of intrarenal infusion of Sar1-Ile8-angiotensin II (3-66 mmol/min, 4 μg/min) were determined in five dogs. This dose of antagonist, which was dissolved in saline and infused at 0.11 ml/min, completely abolished the renal responses to intrarenal injections of 485 pmol (500 ng) of angiotensin II. Others have reported on the blocking potency and intrinsic activity of Sar1-Ile8-angiotensin II (Bravo, Khosla & Bumpus, 1975; Munoz-Ramirez, Khosla, Bumpus & Khairallah, 1975). Variables were measured at intervals during a 40 min control period, a 90 min period of antagonist infusion, and 60 min after stopping the antagonist infusion (recovery). Saline was infused intra-renally (0.11 ml/min) during the control and recovery periods. The same protocol was used in six control dogs except that saline was infused instead of antagonist.

Mean arterial pressure and urine flow were determined with a Statham transducer and a photoelectric drop counter and recorded on a polygraph (Grass). Renal filtration fraction (FF) was determined from the renal arteriovenous extraction of [131I]iothalamate, which was infused intravenously throughout the experiment in a solution of saline at 0.2 ml/min. Glomerular filtration rate (GFR) was calculated according to the formula:

\[ \text{GFR} = \text{FF} \times [\text{renal blood flow} \times (1 - \text{packed cell volume})] \]

This method for measuring glomerular filtration rate has been previously reported (Elwood & Sigman, 1967; Kishimoto, Maekawa, Miyazaki, Yamamoto & Ueda, 1972; Hall & Guyton, 1976). Plasma renin activity was determined by radioimmunoassay of angiotensin I (Haber, Koerner, Page, Kliman & Purnode, 1969) and plasma and urinary electrolytes were determined by flame photometry. Student’s t-test was used for statistical analysis. \( P < 0.05 \) was considered significant.

Results

After 4 days of water deprivation average body weight of the 11 dogs fell from 21.1 to 19.3 kg and average plasma sodium concentration increased from 142 to 154 mmol/l; plasma renin activity averaged 8.44 ng of angiotensin I h\(^{-1}\) ml\(^{-1}\) (SEM 1.82, \( n = 7 \)). Previous values of plasma renin activity in normally hydrated anaesthetized dogs that had been maintained on standard dry dog food and water ad libitum averaged 1.54 ng of angiotensin I h\(^{-1}\) ml\(^{-1}\) (SEM 0.24, \( n = 10 \)).

Large increases in both urine flow and urinary sodium excretion occurred after 60 and 90 min of intrarenal infusion of angiotensin II antagonist (Fig. 1); these changes were significantly greater than those observed in the saline-infused control group. The difference in urine flow changes between the two groups was also significant at 30 min, but 60 min after stopping the antagonist infusion, urine flow and sodium excretion did not differ significantly between the two groups.
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Mean arterial pressure did not change significantly in either group. Renal blood flow and glomerular filtration rate tended to increase in the antagonist group at 60 and 90 min, but these changes were not significantly different from those in the saline-infused control group. However, when the results were analysed by paired analysis within each group, the increases in renal blood flow and glomerular filtration rate were significant at 90 min in the antagonist group but not in the saline-infused group. In the antagonist group, the mean difference from control (ml min⁻¹ g⁻¹ kidney weight ± SEM) for renal blood flow and glomerular filtration rate were 0.65 ± 0.13 (P < 0.01) and 0.12 ± 0.02 (P < 0.01) respectively. The respective values for the saline-infused control group (ml min⁻¹ g⁻¹ kidney weight ± SEM) were 0.15 ± 0.16 (P > 0.3) and 0.03 ± 0.03 (P > 0.3).

Discussion

The results show that in dogs with elevated plasma renin activity due to dehydration intrarenal angiotensin II blockade significantly increases urinary sodium excretion and urine flow. This demonstrates that endogenous angiotensin II has intrarenal actions which lead to salt and water retention. The increase in sodium excretion found in this study probably cannot be explained by the antagonism of aldosterone secretion, since Sar1-Ile8-angiotensin II does not effectively block the steroidogenic properties of angiotensin II at these doses (Bravo et al., 1975). In fact, the dose of Sar1-Ile8-angiotensin II used in the present study has been shown to increase, rather than decrease, plasma aldosterone concentration in normal anaesthetized dogs (Beckerhoff, Ulhschmid, Furrer, Nussberger, Schmied, Vetter & Siegenthaler, 1975).

Freeman et al. (1975) found a statistically significant increase in sodium excretion in sodium-depleted dogs after intrarenal infusion of Sar1-Ala8-angiotensin II, but concluded that this response had no significance since sodium excretion never returned to the control value after cessation of the antagonist. However, since a comparison with a saline-infused control group was not made in that study, the significance of the finding is not known. Mimran et al. (1974) found no change in sodium excretion in sodium-depleted rabbits after intravenous administration of Sar1-Ala8-angiotensin II or SQ 20881, but, as they pointed out, the marked decrease in arterial pressure observed in their experiments may have obliterated any natriuretic response.
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References


