Inhibition of Renin Release in the Dog by Vasopressin and Vasotocin

By Arthur J. Vander

ABSTRACT

In anesthetized dogs the intravenous infusion of arginine vasotocin, 25 mU/min, or vasopressin, 10 mU/min, inhibited renin secretion when control secretion rates were normal or when they were elevated by complete ureteral occlusion. Vasotocin, 5 mU/min, or vasopressin, 1 mU/min, was ineffective. Direct intraarterial infusion of vasotocin, 5 mU/min, into the right kidney inhibited renin secretion by the right kidney only. Glomerular filtration rate and renal plasma flow were not changed, and mean arterial pressure was either not changed or was decreased. Vasotocin caused no change in urine flow but did produce a significant natriuresis secondary to decreased tubular reabsorption. The physiological implications of these polypeptide-renal relationships are discussed.

ADDITIONAL KEY WORDS

posterior pituitary polypeptides
pineal arginine vasotocin angiotensin

Arterial blood was obtained from a femoral artery catheter. Arterial blood pressure was monitored continuously using a Statham gauge and Grass polygraph. Renal secretory and hemodynamic data were obtained by the clearance technique; periods were 10 minutes long with arterial and renal venous blood samples taken in the middle of each period. Creatinine clearance was used as a measure of glomerular filtration rate; total renal plasma flow was determined by the Fick principle, using PAH. In experiments employing complete ureteral occlusion, renal blood flow was measured with a Carolina square-wave electromagnetic flowmeter (model 301) and probe. Experimental observations were not begun until at least 45 minutes after completion of all experimental protocols and administration of priming doses of creatinine and PAH. No fluids other than those described were given.

Protocol 1.—In 7 dogs, after completion of control clearances, an intravenous infusion of arginine vasotocin 1 was begun at the rate of 25 mU/minute. Twenty to 30 minutes later, clearances were again measured, and the vasotocin was stopped. Clearances were measured again during recovery 20 to 30 minutes later. Renin in renal venous blood was measured in only four of the dogs; blood was collected at midpoint of the clearances.

Arginine vasotocin was synthesized by Dr. M. Bodansky, while at the Squibb Institute for Medical Research, and was made available to me by Dr. S. Pavel, Institute of Endocrinology, Bucharest, Romania. The units are rat pressor units.
Protocol 2.—Isotonic saline, 2.5 ml, was injected into the right ureteral catheter, and the catheter was completely occluded. This procedure was used to increase renin secretion above the normal basal levels (2). Twenty minutes later, renal venous blood was obtained and an intravenous infusion of either vasopressin (Pitressin) or arginine vasotocin was begun. The doses used were 1 mU/min (4 dogs) or 10 mU/min (6 dogs) for vasopressin, and 5 mU/min (5 dogs) or 25 mU/min (6 dogs) for vasotocin. Twenty minutes later, additional samples were obtained; the polypeptide was discontinued, and final recovery samples were obtained 20 to 30 minutes later.

Protocol 3.—In three dogs, after obtaining simultaneous control right and left renal venous samples, 2.5 ml saline was injected simultaneously into each ureteral catheter, and both ureters were completely occluded. Ten minutes later, second samples were obtained. The ureters were then released and additional samples obtained 20 to 30 minutes later. An infusion of arginine vasotocin, 5 mU/min, was then begun into the right renal artery and, 2 minutes later, both ureters were again occluded as above. Ten minutes later (12 minutes after beginning the vasotocin) final samples were obtained.

Analytical Procedures
The methods used for determination of sodium, PAH, creatinine, and plasma renin activity have been described in detail previously (2); the only difference in the present experiments was that 0.5 ml of 3.8% NH₄ EDTA was added to the samples prior to incubation, as further protection against angiotensinase. Renin activity is expressed in nanograms of angiotensin-like activity (rat pressor assay) produced per milliliter of plasma during 30 minutes of incubation under standardized conditions. As previously shown (2), changes in renal venous renin may be used to indicate changes in renin release when changes in renal plasma flow do not occur, as in the present experiments. Finally, to validate the use of renin activity (rather than concentration) as a measure of secretion, hog renin (Nutritional Biochemicals Co.) was added to plasma obtained from the same dogs during control periods and during hormone infusion; the amounts of angiotensin generated were identical, thereby establishing that significant changes in neither substrate nor plasma activators or inhibitors were induced by the polypeptides.

Results

Protocol 1.—Data are summarized in Table 1 and Figure 1 (left). Despite the already low control levels of renin release, renal venous renin was significantly reduced even further by vasotocin, 25 mU/min, infused intravenously. This inhibition was completely reversible within 30 minutes after discontinuing the vasotocin. Vasotocin induced no
TABLE 1

Summary of Renal Effects of Vasotocin and Vasopressin Infused Intravenously during Free-Flow or Ureteral Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Vasotocin</th>
<th>Vasopressin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Free flow</td>
<td>Ureteral occlusion</td>
</tr>
<tr>
<td>a Renal venous renin§</td>
<td>-2.0 ± 0.5*</td>
<td>-1.0 ± 0.5</td>
</tr>
<tr>
<td>a Mean arterial BP, mm Hg</td>
<td>3.0 ± 2.5</td>
<td>6.0 ± 4.6</td>
</tr>
<tr>
<td>a Uterine flow (ml/min)</td>
<td>0.00 ± .02</td>
<td>20.7 ± 8.0*</td>
</tr>
<tr>
<td>a Na excretion, µM/min</td>
<td>1.01 ± .03</td>
<td>1.00 ± .02</td>
</tr>
</tbody>
</table>

Statistical analysis is by paired samples. *P < .05; †P < .02; §P < .01. Data are means ± SEM.

§Angiotensin-like activity (ng/ml). RPF = total renal plasma flow; GFR = glomerular filtration rate.

-significant changes in mean arterial blood pressure, glomerular filtration rate, renal plasma flow, or urine flow. PAH extraction ratio was also not altered. The increase in urinary sodium excretion was statistically significant for the entire group; however, two of seven dogs failed to show an increase, although renal venous renin was decreased. These two dogs had extremely low control rates of sodium excretion, 2.0 and 3.3 µM/min.

Protocol 2.—Data are summarized in Table 1 and Figure 1 (middle and right). The increased renin release induced by ureteral occlusion was significantly inhibited both by vasopressin, 10 mU/min, and by vasotocin, 25 mU/min. At 1 mU/min and 5 mU/min, respectively, these hormones did not inhibit renin release. Renal plasma flow was not significantly changed. The only significant change in mean arterial pressure was the reduction induced by the higher infusion rate of vasotocin.

Protocol 3.—Data are summarized in Figure 2. The increases in renin release induced by ureteral occlusion were the same for the right and left kidneys when no hormone was given. However, during vasotocin infusion directly into the right renal artery, ureteral occlusion induced a much greater increase in renal venous renin from the left than from the right kidney in all three dogs. Indeed, right renal venous renin actually decreased during ureteral occlusion in one dog receiving vasotocin.

Discussion

These data confirm the report of Bunag, Page, and McCubbin (1) that renin release can be inhibited by vasopressin. The infusion rates used by these investigators were 1 to 4 mU/kg/min. In this study, inhibition was obtained with 10 mU/min, approximately the same as their lower doses. Inhibition was not
observed with 1 mU/min, and no further attempt was made to determine the actual minimal effective dose, for reasons which will be apparent from the following analysis. A critical question raised by this ability of vasopressin to inhibit renin release is whether such inhibition actually occurs under physiological conditions. If one assumes a half life of 6 minutes (3) and a volume of distribution of 100 ml/kg body weight (3), then the infusion of 10 mU/min would increase plasma vasopressin by approximately 50 μU/ml. Studies by Share (4) have demonstrated that such increments do occur in the intact animal subjected to volume depletion. Moreover, the failure of 1 mU/min, a high dose relative to the normal rates of vasopressin secretion, to inhibit renin secretion does not really indicate that this effect occurs only in such abnormal circumstances as hemorrhage. The expected increment in plasma vasopressin (5 μU/ml) induced by the infusion of 1 mU/min probably represents only a very small relative increase in my dogs, since, under the experimental conditions (antidiuresis, pentobarbital anesthesia, and laparotomy), endogenous plasma vasopressin would likely already be 5 to 10 times higher. Thus, to be more meaningful physiologically, the dose-response relationship between plasma vasopressin and renin secretion will have to be determined in unanesthetized, unstressed dogs and include actual measurements of plasma vasopressin concentrations. Such experiments are in progress.

One reason for studying vasotocin was that it is structurally intermediate between vasopressin and oxytocin. Oxytocin was reported by Bunag, Page, and McCubbin (1) to have little effect on renin release even when infused in amounts ten times larger (by weight). This observation coupled with the present finding that vasotocin is almost as potent (vasopressin and vasotocin units per weight are approximately similar) as vasopressin suggests that the presence of a strong basic amino acid in the polypeptide side-chain is essential for the inhibitory effect.

A second reason for evaluating the effects of vasotocin was the recent discovery (5, 6) that this hormone, which is absent from the mammalian neurohypophysis, is present in the mammalian pineal body (cow and pig). Numerous studies (7) have suggested a relationship between the pineal body, salt balance in general, and aldosterone secretion in particular. The present finding that vasotocin can inhibit renin secretion may have important bearing on these relationships. However, there is now virtually no information as to whether vasotocin really does circulate in the blood in mammals.

The experiments of protocol 3 clearly demonstrate that the inhibitory effect, at least of vasotocin, is exerted directly on the kidney. However, the precise mechanisms by which this effect is exerted cannot be determined from these experiments. The absence of increased blood pressure, renal plasma flow, or glomerular filtration rate constitutes strong evidence against a possible effect on any intrarenal baroreceptor. Indeed, the inhibition induced by the higher dose of vasotocin was actually associated with a fall in blood pressure, probably secondary to a decrease in plasma angiotensin. The increased sodium excretion induced by vasotocin is similar to that previously reported for dogs by Chan and Sawyer (8); the effect is apparently on tubular reabsorption since the glomerular filtration rate was not increased. It is possible, therefore, that vasotocin and vasopressin, which has also been reported to be mildly natriuretic under appropriate conditions (8, 9), might alter macula densa function either directly or indirectly by inhibiting proximal or loop sodium reabsorption, thereby altering the load of sodium entering it (10). This natriuretic effect of vasotocin is of particular interest in light of the recent demonstration (11) that a natriuretic hormone is produced by the brain. Finally, the possibility of a direct effect on the granular cells must be considered.

Acknowledgment

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