Endogenous Angiotensin Stimulation of Vasopressin in the Newborn Lamb

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ABSTRACT The effect of furosemide on plasma renin, vasopressin (AVP), and aldosterone concentrations was studied in 10 control and 6 nephrectomized lambs during the 1st 2 wk of life. In a separate study in 10 newborn lambs, 1-sarcosine-8-alanine-angiotensin II (saralasin acetate, 5 μg/kg per min) was infused alone for 40 min, after which furosemide 2 mg/kg i.v. was injected in association with continuing saralasin acetate infusion.

Plasma renin activity increased from a mean (±SEM) of 21.3±3.4 ng/ml per h in the 10 control lambs to 39.4±8.2 ng/ml per h at 8 min ($P < 0.001$) and remained high through 120 min after furosemide. Plasma AVP and aldosterone concentrations increased from respective mean values of 2.1±0.4 μU/ml and 12.8±2.5 ng/dl to 9.8±2.0 μU/ml ($P < 0.01$) and 23.0±7.7 ng/dl ($P < 0.05$) at 35 min and 13.8±2.1 μU/ml and 23.0 ±4.4 ng/dl at 65 min after furosemide (each $P < 0.01$). There was an insignificant AVP response in the 10 lambs treated with angiotensin inhibitor: from a mean base line of 4.7±0.9 to 8.3±2.0 μU/ml at 35 min, and 7.4±2.0 μU/ml at 65 min after furosemide. There was no increase in AVP in the anephric lambs.

The mean increment AVP response from base line in the newborn lambs without saralasin, Δ 10.8±2.0 μU/ml, was greater than in the lambs with saralasin, Δ4.0±1.9 ($P < 0.05$), and greater than in the anephric lambs, Δ3.3±2.1 μU/ml ($P < 0.05$). The mean blood pressure fell 6 mm Hg in the 10 control lambs ($P < 0.05$), 7 mm Hg in the anephric lambs ($P < 0.05$), and 16 mm Hg in the lambs treated with angiotensin inhibitor ($P < 0.05$) by 35 min after furosemide. However, the changes in plasma AVP were not related to the fall in blood pressure.

These data support the view that the observed AVP response to furosemide in the newborn lamb was mediated through the renin-angiotensin system.

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INTRODUCTION

Intravenous administration of pressor amounts of angiotensin II in the conscious dog (1, 2) or intracarotid infusion in the anesthetized dog (3) provokes an increase in plasma vasopressin (AVP)[1] concentration. Ventriculo-cisternal applications of renin or angiotensin also can increase plasma AVP (2–5). Recently, it has been shown that centrally administered renin evokes marked dipsogenic and pressor effects mediated via formation of angiotensin II within the central nervous system (6, 7). Other studies have failed to confirm that angiotensin II stimulates AVP release. Blood levels of bioassayable AVP did not rise during systemic angiotensin II infusions in anesthetized dogs (8), in dogs during modest hemorrhage (9), or in human subjects during fluid ultrafiltration from hemodialysis (10) when base-line endogenous renin and angiotensin levels were elevated. Moreover, the plasma renin activity (PRA) responses to postural change and to salt depletion in man have been reported not to be associated with increased plasma antidiuretic activity (11); and angiotensin II infused into human subjects failed to alter renal water excretion (12). There is no definitive evidence for a role of endogenous renin in AVP stimulation under any conditions in any age group.

The renin-angiotensin system is activated in the newborn, and PRA, angiotensin II, and aldosterone concentrations are high in the neonatal period (13, 14). We have shown that furosemide will evoke increases in plasma PRA and aldosterone levels (14) as well as intense thirst-like behavior in the newborn lamb. Therefore, the newborn lamb seemed an appropriate model to study endogenous renin-angiotensin and AVP interaction.

METHODS

10 normal and 6 nephrectomized newborn lambs were studied during the 1st 2 wk of life. The nephrectomized lambs were

[1] *Abbreviations used in this paper*: AVP, vasopressin; PRA, plasma renin activity.

studied 24–30 h after surgery. Furosemide 2 mg/kg i.v. was infused over 1–2 min. In a separate study in 10 normal lambs, 1-sarcosine-8-alanine-angiotensin II (saralasin acetate, 5 μg/kg per min) was infused alone for 40 min, after which furosemide 2 mg/kg i.v. was injected in association with the continuing saralasin acetate infusion for an additional 125 min. The lambs were not allowed to drink during any of the studies. Water intake (5% glucose in water) by nipple and baby bottle was measured in a separate study conducted in 3 newborn lambs.

Blood samples for PRA, plasma aldosterone, plasma AVP, plasma sodium and osmolality, and hematocrit were drawn before the study (−10 and −5 min), during the saralasin alone infusion (at 30 and 40 min in group II animals), and at 8, 20, 35, 65, and 125 min after furosemide infusion. Blood pressure was measured continuously with a water manometer (15). Timed urine samples were collected for Na and K measurements before and 30 min after furosemide. PRA was measured by generation of angiotensin I, which was then measured by radioimmunoassay (16, 17). AVP (18, 19) after extraction with bentonite, and aldosterone (20) after column chromatography were measured by radioimmunoassay. Antiserum R-71 was used for radioimmunoassay of AVP at a final dilution of 1:300,000 (18, 19); the limit of detection (defined as the smallest quantity of hormone statistically separable from assay tubes without added hormone) was 0.4 μU/ml. The intra-assay and interassay coefficients of variation were 4.5 and 8.1%. Assay characteristics have been described in detail elsewhere (19). Sodium and potassium were measured by flame photometry, osmolality by digital osmometer. The potassium EDTA collection tubes add 20 mosmol/liter to the measured plasma osmolality vs. serum osmolality; a uniform volume of blood was added to these tubes.

Mean results were compared by paired t test.

RESULTS

Table I shows the PRA response to furosemide in normal lambs with and without saralasin acetate and in the anephric lambs without saralasin acetate. Base-line (mean±SEM) PRA was 21.3±3.4 ng/ml per h in the normal lambs without the angiotensin inhibitor and increased to 39.4±8.2 ng/ml per h at 8 min ($P < 0.001$). Values remained significantly elevated above base-line through 125 min (Table I). The mean base-line plasma aldosterone concentration of 12.8±2.5 ng/dl increased to 23.0±7.7 at 35 min ($P < 0.05$) and 23.0 ±4.4 ($P < 0.01$) ng/dl at 65 min after furosemide, and fell to 15.2±3.1 ng/dl at 125 min. Individual values peaked at 35 or 65 min. During continuous infusion of angiotensin inhibitor alone, mean PRA increased from a base-line level of 22.3±6.0 ng/ml per h to 84.5 ±14.5 and 89.8±14.6 ng/ml per h at 30 and 40 min, respectively (both $P < 0.001$) (Table I); no further increase in PRA was observed after furosemide. PRA did not increase in the anephric lambs stimulated with furosemide (Table I).

Table II shows the AVP responses to furosemide in the 10 control lambs, in the 10 newborn lambs infused continuously with saralasin acetate, and in the 6 anephric lambs without the angiotensin inhibitor. The mean base-line plasma AVP concentration, 2.1±0.4 μU/ml, increased to 10.8±2.0 at 35 min, and 13.8±2.1 μU/ml at 65 min after infusion, and fell to 8.7±1.5 μU/ml at 125 min after infusion. These mean values at 35–125 min were significantly higher than the base-line concentration (each $P < 0.01$). Plasma AVP levels in individual animals peaked at either 35 or 65 min after furosemide.

The mean plasma AVP concentration in the normal lambs was not altered by continuous infusion of saralasin acetate alone for 40 min. (Table II). In these animals, during continuous saralasin acetate infusion, mean plasma AVP concentrations rose after furosemide; from a mean of 4.7±0.9 to 8.3±2.0 μU/ml at 35 min, and 7.4±2.0 μU/ml at 65 min after furosemide; but these values were not significantly higher (all P values < 0.05) than the base-line level (4.7±0.9 μU/ml). Nor

TABLE I

*PRA Response to Furosemide in Newborn Lambs with and Without Saralasin and in Anephric Lambs**

	No. of animals	PRA							
		Base line	Saralasin alone, *min*		During furosemide, *min*				
			30	40	8	20	35	65	125
		ng/ml/h							
Newborn lambs without saralasin	10	21.3 ±3.4	—	—	39.4 ±8.2§	44.6 ±6.6§	46.8 ±7.3§	53.6 ±9.3§	56.1 ±8.5§
Newborn lambs with saralasin‡	10	22.3 ±6.0§	84.5 ±14.5§	89.8 ±14.6§	95.9 ±12.5§	91.5 ±13.4§	81.3 ±14.8§	67.3 ±10.0§	54.5 ±2.0§
Anephric lambs without saralasin	6	6.5 ±1.4	—	—	5.1 ±1.7	5.1 ±1.9	4.6 ±1.0	4.1 ±1.7	3.3 ±1.5

* Values recorded as mean±SEM.

‡ Saralasin plus furosemide infused for last 125 min.

§ $P < 0.001$ vs. base line.

TABLE II

*AVP Response to Furosemide in Normal Lambs, Lambs Treated with Saralasin, and in Anephric Lambs without Saralasin**

	No. of animals	Plasma AVP concentration						
		Base line	Saralasin alone, *min* (30 + 40)	Furosemide, *min* 8	20	35	65	125
				μU/ml				
Newborn lambs without saralasin	10	2.1±0.4	—	2.8±0.6	5.0±1.4	10.8±2.0§	13.8±2.1§	8.7±1.5§
Newborn lambs with saralasin‡	10	3.0±0.6	4.7±0.9	4.6±1.2	5.3±1.2	8.3±2.0	7.4±2.0	6.8±2.0
Anephric lambs without saralasin	6	6.6±3.4	—	6.7±5.0	8.7±6.5	9.7±7.5	10.6±8.2	11.0±8.9

*D** Values recorded as mean±SEM.

‡ Saralasin plus furosemide for last 125 min.

§ $P < 0.01$.

did mean plasma AVP levels increase significantly in response to furosemide in the anephric lambs (Table II). The mean increment AVP response from base line in the newborn lambs without saralasin acetate, (Table III) Δ 10.8±2.0 μU/ml, was greater than in the lambs with saralasin, Δ 4.0±1.9 μU/ml ($P < 0.05$), and greater than in the anephric lambs, Δ 3.3±2.1 U/ml ($P < 0.05$).

Systemic blood pressure (Table IV) fell slightly in both control and anephric lambs (a mean of 6 and 7 mm Hg, $P < 0.05$, respectively) 35 min after furosemide infusion. The blood pressure dropped a mean of 9 mm Hg during the constant infusion of saralasin acetate alone ($P < 0.05$) and another 7 mm Hg ($P < 0.05$) 35 min after furosemide plus saralasin acetate in the newborn lambs.

The mean base-line plasma sodium was 138±1.4 meq/liter in the control group, (Table V) 139±1.2 in the saralasin group, and 131±2 in the anephric group (control vs. anephric $P < 0.05$). The mean plasma osmolality was 295±3.4 mosmol/liter in the control group, 297 ±3.5 in the saralasin group, and 323±9 mosmol/liter in the anephric group (control vs. anephric $P < 0.01$).

TABLE III

AVP Response to Furosemide in Normal Lambs, Lambs Treated with Saralasin and Anephric Lambs without Saralasin

Groups	Base line to peak response
	μU/ml
Newborn lambs without saralasin	Δ 10.8±2.0*
Newborn lambs with saralasin	Δ 4.0±1.9
Anephric lambs without saralasin	Δ 3.3±2.1

$P < 0.01$. Normal vs. saralasin, $P < 0.05$. Normal vs. anephric, $P < 0.05$.

* Mean±SEM.

There were no changes in sodium or osmolality during the 125-min study period in any of the groups.

Thirst-like behavior was observed between 9 and 20 min after furosemide in the control lambs. In a separate study in three normal lambs water intake increased at 30 min after furosemide from a mean of 4±1 to 40±6 ml/30 min.

Urine volume and urine sodium excretion for 30-min intervals before and after furosemide was similar in the normal lambs and saralasin-treated lambs (Table VI). The most marked diuresis occurred during the first 60 min after furosemide.

DISCUSSION

The present results, in agreement with our earlier observations, show that acute injection of furosemide will increase PRA and plasma aldosterone concentrations in the newborn lamb (Table I) (14). In addition, furosemide produces a marked increase in plasma AVP concentrations (Table II). The timing of the AVP response is similar to that of the plasma aldosterone response to furosemide, suggesting that the increase in plasma AVP may be mediated by a direct action of the renin angiotensin system on the hypothalamic-neurohypophysial system. However, furosemide injection was followed by a small but significant fall in mean arterial blood pressure (6 mm Hg, Table IV) 35 min after injection. Thus, it is possible that the AVP response to furosemide in these newborn animals was mediated via hemodynamic changes sensed either by carotid-aortic baroreceptors or left atrial stretch receptors.

Two further studies were conducted to resolve these possibilities: furosemide was administered to anephric newborn lambs, and furosemide was injected into normal lambs infused continuously with an angiotensin inhibitor (saralasin). The increase in mean plasma AVP concentration in response to furosemide in the aneph-

TABLE IV

*Systemic Arterial Blood Pressure in Newborn Lambs with and without Saralasin and Anephric Lambs Infused with Furosemide**

	No. of animals	Blood pressure							
		Base line	Saralasin alone, *min*		Furosemide, *min*				
			30	40	8	20	35	65	125
		mm Hg							
Newborn lambs without saralasin	10	82.0±1.4	—	—	81.0±1.8	79.0±1.6	76.1±1.3§	74.6±1.1§	74.1±2.0§
Newborn lambs with saralasin‡	10	82.2±3.7	72.3±5.0	72.0±4.9	72.1±4.8	67.3±5.0	64.9±3.5§	64.0±3.4§	64.9±3.2§
Anephric lambs without saralasin	6	77.0±3.0	—	—	74.5±2.5	70.0±4.0	69.0±4.0§	71.0±2.5§	70.0±3.0§

* Values recorded as mean±SEM.
‡ Saralasin plus furosemide infused for last 125 min.
§ $P < 0.05$ vs. base line.

TABLE V

*Changes in Plasma Sodium, Osmolality, and Hematocrit after Furosemide in the Newborn Lamb**

	Base line	Saralasin alone, *min*		Furosemide, *min*				
		30	40	8	20	35	65	125
Control lambs (n = 10)								
Plasma Na, *meq/liter*	138 ±1.4	—	—	138 ±1.1	139 ±1.4	138 ±1.3	138 ±1.2	139 ±1.3
Plasma osmolality,‡ *mosmol/liter*	295 ±3.4	—	—	293 ±4.8	293 ±3.6	295 ±4.0	294 ±4.0	295 ±3.7
Hematocrit, %	32.2 ±2.4	—	—	32.6 ±3.2	32.0 ±2.9	32.6 ±3.7	32.3 ±3.3	32.3 ±2.8
Lambs treated with saralasin acetate (n = 10)								
Plasma Na, *meq/liter*	139 ±1.2	139 ±1.2	140 ±1.3	139 ±1.0	140 ±2.0	139 ±2.1	139 ±1.4	140 ±1.5
Plasma osmolality,‡ *mosmol/liter*	297 ±3.5	298 ±2.4	297 ±3.4	298 ±3.1	297 ±3.4	296 ±3.2	297 ±3.2	298 ±3.4
Hematocrit, %	32.5 ±3.0	32.0 ±2.9	32.7 ±3.1	32.0 ±2.9	32.7 ±3.1	32.2 ±2.9	33.0 ±2.8	32.2 ±2.9
Anephric lambs								
Plasma Na, *meq/liter*	131 ±2§	—	—	130 ±3	130 ±2	131 ±2	130 ±2	130 ±2
Plasma osmolality,‡ *mosmol/liter*	323 ±9‖	—	—	323 ±11	324 ±10	324 ±8	322 ±12	321 ±12
Hematocrit, %	32.8 ±1.7	—	—	33 ±1.8	32.8 ±1.9	32.6 ±1.8	32.2 ±1.6	32.2 ±1.5

* Values recorded as mean±SEM.
‡ Uncorrected plasma osmolality.
§ $P < 0.05$ vs. control lamb values.
‖ $P < 0.01$ vs. control lamb values.

TABLE VI

*Urine Output after Furosemide Infusion vs. Normal Lambs**

Time after furosemide infusion, *min*	30	0–30	30–60	60–90	90–120
Control					
Fluid, *ml/kg*	0.8±0.1	9.9±2.1	9.2±1.9	4.6±0.7	2.0±0.5
Sodium, *meq/kg/liter*	1.4±0.1	9.3±1.4	9.4±1.1	4.7±1.2	5.5±1.5
Saralasin-treated					
Fluid, *ml/kg*	1.4±0.4	10.2±2.0	9.8±1.8	5.1±1.1	2.2±0.6
Sodium, *meq/kg/liter*	1.6±0.2	9.7±1.5	10.0±1.6	4.3±1.2	5.0±1.4

* All values are mean±SEM.

ric lambs was insignificant (Table II). The 35- and 65-min plasma AVP concentrations after furosemide (8.3±2.0 μU/ml at 35 min, and 7.4±2.0 μU/ml at 65 min) in the 10 newborn lambs during infusion of angiotensin inhibitor alone (Table II) were not statistically different from the base-line concentration (4.7±0.9 μU/ml) despite maximum PRA stimulation (Table I). Thus, the data strongly suggest that the angiotensin inhibitor effectively antagonized the AVP response to furosemide, and nephrectomy eliminated the response.

The AVP responses to furosemide were not correlated with the mean basal plasma osmolality and plasma sodium, and sodium and osmolality were comparable in control and angiotensin inhibitor-treated animals. The basal plasma sodium was lower ($P < 0.05$) and osmolality higher ($P < 0.01$) in the anephric lambs than in the control animals (Table V), but these parameters again were not correlated with the AVP responses. The effective plasma osmolality caused by sodium in the nephrectomized lambs was lower than in the normal or saralasin-treated animals. This decreased effective plasma osmolality might have suppressed base-line AVP levels (21), but it is unlikely that it suppressed the response to furosemide. Recent studies in our laboratory[2] have shown that water loading changes base-line AVP but does not inhibit the increase in AVP after hemorrhage. Its effect on nonosmotic stimulation is not known. The mean basal plasma AVP level in the nephrectomized lambs (6.6 ±3.4 μU/ml) was higher than in the control lambs; it is unclear whether this represents increased secretion or decreased clearance of AVP. The water and salt diuresis (Table VI) could be calculated to have depleted the extracellular fluid volume ≅5% by 30 min, 10% by 60 min, and 12% by 90 min after furosemide. These losses were not correlated with plasma AVP levels in the control group, which peaked at either 30 or 60 min and decreased by 120 min after furosemide. Plasma AVP concentrations did not increase significantly in the animals given furosemide plus saralasin, in spite of a diuresis similar in magnitude to that induced by furosemide in control animals.

There was no correlation between the fall in blood pressure and the AVP responses (Tables II, IV). The mean 7-mm Hg reduction in blood pressure in the angiotensin inhibitor-treated animals after furosemide was similar at 35 min to the 6-mm Hg reduction 35 min after furosemide in control animals (Table IV), whereas the mean peak AVP response at 35 or 65 min was much greater in the control lambs (Δ 10.8±2.0 vs. Δ 4.0±1.9 μU/ml, Table III, $P < 0.05$). Also, a mean blood pressure drop of 7 mm Hg in the nephrectomized lambs 35 min after furosemide (Table IV) did not produce a significant rise in plasma AVP (Table III), (Δ 3.3±2.1 compared to Δ 10.8±2.0 μU/ml in the control group, $P < 0.05$). Finally, the mean blood pressure fall of 9 mm Hg during the constant infusion of angiotensin inhibitor alone (Table IV) was not associated with a significant change in plasma AVP concentration (Table II). The fact that the AVP response to furosemide is ablated by either nephrectomy or saralasin acetate infusion, coupled with the observation that the AVP response can be dissociated from the fall in blood pressure, supports the view that angiotensin II mediates AVP release, as well as aldosterone secretion, after furosemide stimulation. The mean base-line osmolality and AVP levels were higher in the anephric than in control animals (323±9 vs. 295±3.4 mosmol/liter, and 6.6±3.4 vs. 2.1±0.4 μU/ml, respectively), and the variance of the AVP levels in the anephric animals were consistently high (Table II). Several of these animals, which were uremic and variably dehydrated had high base-line plasma AVP concentrations; however, there was no PRA or AVP response to furosemide in any of the six animals.

The mechanism of angiotensin II stimulation of AVP release is not entirely clear. The fact that cerebral intraventricular injection of angiotensin II promptly stimulates AVP release (2–5) suggests a direct action of this peptide on the hypothalamic system. This hypothesis is further supported by the observation that when saralasin is infused directly into a cerebral ventricle, the AVP response to intraventricular renin or angio-

[2] Weitzman, R., and D. A. Fisher. Unpublished observations.

tensin II is totally inhibited (4, 6, 7). Both angiotensin (22) and saralasin (23) cross the blood-brain barrier; and a high enough dose of saralasin, given peripherally, will inhibit the central effects of angiotensin II (23).

The mechanism of action of furosemide on blood pressure is not clear. The fact that furosemide lowered blood pressure (Table IV) in the absence of salt and water diuresis in anephric lambs suggests that the drug acts directly on vascular tone or through prostaglandins (24, 25). The observation that saralasin acetate and furosemide induced hypotension in the normal animals or the furosemide induced hypotension in the anephric animals did not provoke significant vasopressin release (Tables II, IV) suggests that such hypotension is a minimal stimulus to the atrial stretch receptors or the aortic arch and carotid sinus baroreceptors modulating vasopressin release. A similar observation has been reported recently by Anderson et al. (26), who noted that infusion of saralasin into cirrhotic patients produced hypotension associated with a fall in plasma antidiuretic hormone levels.

The role of renin-angiotensin-vasopressin interaction in water and electrolyte homeostasis is unclear. Angiotensin has been shown in man to potentiate the AVP response to an osmolar stimulus (27, 28), conversely Claybaugh (29) showed that hyperosmolality augmented the AVP response to renin infusion in conscious dogs. Thus the angiotensin-AVP interaction would tend to reinforce the defense of dehydration. In addition, angiotensin has been shown to stimulate thirst (6, 30, 31), an important physiologic mechanism to help maintain water balance. Thirst-like behavior was consistently observed between 8 and 20 min after furosemide in the control animals in the present study and this was documented by a measured increase in fluid intake. Finally AVP administration has been shown to suppress renin release (32–34). This effect also has been well documented in infants and is known to be associated with natriuresis (35). This evidence, coupled with the present observation that endogenous angiotensin II evokes AVP secretion, suggests that renin-angiotensin-AVP interaction may be important in the modulation of salt and water homeostasis.

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