Decreased Vascular and Increased Adrenal and Renal Sensitivity to Angiotensin II in the Newborn Lamb

SHARON R. SIEGEL

SUMMARY The effects of two doses of angiotensin II (0.025 µg/kg per min and 0.25 µg/kg per min) on plasma renin activity (PRA), aldosterone concentration, creatinine clearance, and sodium and potassium excretion were studied in two groups of 2- to 3-week-old lambs. The 0.025 µg/kg per min dose of angiotensin II also was studied in six adult ewes. In response to the angiotensin II infusions, PRA decreased in the newborns from baselines of 24.5 ± 2.3 ng/ml per hr (mean ± SE) and 22.9 ± 3.5 to 13.6 ± 0.8 and 13.0 ± 2.2 at 30 minutes (P < 0.01), respectively, and returned to baseline at 60 minutes; PRA decreased from 1.7 ± 0.1 to 0.95 ± 0.3 ng/ml per hr at 30 minutes (P < 0.01) in the ewe and returned to baseline at 60 minutes. Plasma aldosterone increased in the newborns from baselines of 17.4 ± 5.0 ng/dl and 14.7 ± 3.9 to 33.1 ± 6.9 and 32.5 ± 6.3, respectively, at 15 minutes (P < 0.01) and returned to baseline at 60 minutes. Plasma aldosterone increased from 4.3 ± 0.7 to 9.2 ± 2.0 ng/dl in the ewe, and returned to baseline at 60 minutes. The change in the PRA and aldosterone responses from baseline to peak for the low and high angiotensin dose was similar in the newborn lambs and greater than in the ewe (P < 0.01). There was no change in the creatinine clearance, plasma sodium, or hematocrit. Urine sodium excretion increased from 0.16 ± 0.04 total mEq/30 min to 0.87 ± 0.27 (P < 0.05) in the newborns during the 0.25 µg/kg per min angiotensin II infusion. We conclude that, under basal conditions, the newborn lamb has high PRA and aldosterone levels with decreased pressor and increased aldosterone and renin release responsiveness to angiotensin II compared to the adult. Circ Res 48: 34-38, 1981

BLOOD pressure in the newborn is relatively low compared to the adult (Broughton-Pipkin and Symonds, 1977). Little is known about blood pressure regulation and responsiveness in the newborn. In the adult, pressor responsiveness varies with sodium and potassium balance (Hollenberg et al., 1975; Reid and Laragh, 1965), plasma renin and angiotensin II levels (Chinn and Dusterdieck, 1972), and prostaglandin concentrations (Hall et al., 1978). Adrenal aldosterone release responsiveness to ACTH, angiotensin II, and potassium seems to be positively dependent both on the steady state (Sealey et al., 1978) and acute level of angiotensin II (Hollenberg et al., 1974; Oelkers et al., 1975). Kidney renin content and renin release are augmented with high levels of angiotensin II (Flamenbaum and Hamburger, 1974; Fray, 1978).

The newborn human and lamb have high plasma levels of renin and angiotensin (Broughton-Pipkin and Symonds, 1977; Kotchen et al., 1972; Siegel and Fisher, 1977). The purpose of this study was to determine the pressor, aldosterone, and renin release response to angiotensin II in the newborn lamb and to compare them to those of the adult ewe.

Methods

Six newborn lambs (group 1) (8-10 kg) and six ewes (45-50 kg) were treated with a continuous infusion of exogenous angiotensin II at 0.025 µg/kg per min and seven lambs (group 2) with 0.25 µg/kg per min. The lambs, with their nursing mothers, were obtained from the vivarium. Polyvinyl catheters were inserted into the carotid artery and jugular vein or femoral artery and/or vein under local anesthetic (1% lidocaine). The animals were restrained on a specially constructed board so that they were non-stressed and studied 2 days after catheter placement. The lambs were kept warm and quiet during the short study at 2–3 weeks of age. Polyvinyl catheters also were inserted into the carotid artery and jugular vein of the ewes under local anesthetic (1% lidocaine), and the animals were studied in their cages 2 days after catheter placement.

Two baseline blood samples were drawn 10 minutes apart for determination of plasma renin activity (PRA) and plasma aldosterone level. These were followed by a 30-minute angiotensin infusion. Repeat blood samples were drawn at 5, 15, and 30 minutes after the start of the infusion and 30 minutes after stopping. Less than 3% of the blood volume was removed and the blood was replaced.
with isotonic saline. The first urine sample was discarded and subsequent 30-minute urine collections were collected by catheter for measurement of sodium, potassium, and creatinine throughout the study. Blood for determination of creatinine, sodium, and potassium was collected at the middle of each 30-minute urine collection period. Aortic blood pressure was monitored continuously with a Statham transducer (P 23) and a Gould blood pressure recorder.

For measurement of PRA, the blood samples were collected in KEDTA (150 µg/ml whole blood) at room temperature. To 1.0 ml of plasma, 10 µl of 6.6 g/100 ml 8-OH quinoline, 10 µl of 10 g/100 ml BAL, and 10 µl of 3 g/100 ml O-phenanthroline were added to inhibit converting enzyme and angiotensinase. Twenty-five microliters of 4.0 M Tris phosphate-Tris maleate buffer, pH 6.2, were added to reach a pH of 6.5 for maximal generation of angiotensin I in sheep blood. The plasma was divided into two aliquots, one for a blank (frozen) and the other for generation of angiotensin I at 37°C for 1 hour. Plasma renin activity (generated angiotensin I) was measured by radioimmunoassay (Haber et al., 1969). Aldosterone, after column chromatography, was measured by radioimmunoassay (Ito et al., 1972). The coefficient of intra-assay variation was 8% and inter-assay variation, 10%. Sodium and potassium were measured by flame photometry. Creatinine clearance was measured by the method of Folin and Wu (1919). Statistics were measured by analysis of variance and Student's t-test. Results are expressed as mean ± SE.

**Results**

Table 1 shows the increase in mean aortic blood pressure following infusion of angiotensin into the newborn lambs and ewes. No increase in blood pressure was noted in newborn lambs receiving angiotensin II at 0.025 µg/kg per min (group 1). At angiotensin II, 0.25 µg/kg per min, group 2 lambs raised their blood pressure to an extent similar to that of ewes which received the lower (0.025 µg/kg per min) angiotensin II dose.

<table>
<thead>
<tr>
<th>TABLE 1  The Effects of Angiotensin II on Blood Pressure in the Newborn Lamb and Ewe</th>
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<tbody>
<tr>
<td><strong>Newborn lamb</strong></td>
</tr>
<tr>
<td>Basal mean arterial blood pressure (mm Hg)</td>
</tr>
<tr>
<td>Change in mean arterial blood pressure (mm Hg)</td>
</tr>
<tr>
<td><strong>Ewe</strong></td>
</tr>
<tr>
<td>Basal mean arterial blood pressure (mm Hg)</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE.
FIGURE 2  Plasma aldosterone increased in groups 1 and 2 after 15 minutes of the angiotensin II infusions (0.025 and 0.25 μg/kg per min) (P < 0.01) and in the ewe after angiotensin II (0.025 μg/kg per min) (P < 0.05) and returned to baseline at 60 minutes.

PRA and aldosterone was similar in group 1 (0.025 μg/kg per min angiotensin II) and group 2 (0.25 μg/kg per min angiotensin II) (Table 2). The change in response from baseline to peak for PRA and aldosterone was greater in the newborn lamb than the ewe (P < 0.01) at the same angiotensin II dose.

The plasma sodium levels, 138 ± 1, 138 ± 1, and 140 ± 1 mEq/liter, in groups 1, 2, and the ewes, respectively, did not change during the study.

Table 3 shows results of the three 30-minute urine collection periods, (−30 minutes) before, (+30 minutes) during, and (+30−60 minutes) after the angiotensin II infusion. The decrease in creatinine clearance, ml/min, in period 2 (+30 minutes) during the low and high dose angiotensin II infusions in the newborn lambs was not statistically significant. Data for period 3 were similar to those for period 1. Urine sodium excretion increased from 0.16 ± 0.04 total mEq/30 min to 0.87 ± 0.27 (P < 0.05) in the newborn lamb during the 0.25 g/kg per min angiotensin II infusion. There was no significant change in potassium excretion with either dose of angiotensin II.

**Discussion**

The newborn lamb showed no pressor response (Table 1) to the low dose of angiotensin II (0.25 μg/kg per min), which raised the ewes' blood pressure by 33 ± 2.2 mm Hg. It required 10 times the concentration of angiotensin II (0.25 μg/kg per min) to raise the blood pressure of the newborns by 32 ± 1.1 mm Hg. These data show that the newborn lamb has a lesser pressor response to angiotensin II than the ewe. The decreased pressor responsiveness in the newborn may be due to receptor sensitivity depression from previous exposure to the high endogenous renin-angiotensin II levels. Pressor responsiveness to angiotensin II has been shown to decrease with an increase in plasma renin and angiotensin II levels (Chinn and Dusterdieck, 1972). Similar mechanisms have been observed in response to other hormones and drugs (Tell et al., 1978).

The reasons for the high renin-angiotensin-aldosterone levels in the newborn human and lamb are not clear. The metabolic clearance rates of PRA in the immature lamb and adult ewe are similar, both showing a two-compartment disappearance curve (Oakes et al., 1977). The metabolic clearance rate of aldosterone/body surface area is similar in the young and adult (Koworski et al., 1974) with an increase in aldosterone secretion rate. Renin substrate is only slightly elevated in the newborn compared to the adult, and the high PRA levels are related primarily to an increase in plasma renin concentration (Godard et al., 1976). The newborn lamb nurses and, therefore, receives a low sodium (6-7 mEq/l) and potassium (13 mEq/l) intake, as does the human (Siegel and Oh, 1976). Graystone (1968) compared sodium turnover in infants, children, and adults and showed that low sodium intake could not be the sole explanation of the increased PRA in the young. The immature lamb (Robillard et al., 1977), like the human (Cheek et al., 1961; Siegel and Oh, 1976), has impaired conservation of sodium; there is less efficient proximal tubular reabsorption of sodium (Solom, 1974), resulting in a natriuresis during the early newborn period. There is also a relative contraction of effective extracellular fluid volume (Fris, 1961). The sodium-dependent regulatory mechanism for aldosterone secre-

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**TABLE 2  The Effects of Angiotensin II on PRA and Aldosterone in the Newborn Lamb and Ewe**

<table>
<thead>
<tr>
<th></th>
<th>Baseline to peak response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRA (ng/ml per hr)</td>
</tr>
<tr>
<td><strong>Newborn 0.025 μg/kg per min Angiotensin II</strong></td>
<td>Δ11.1 ± 2.2*</td>
</tr>
<tr>
<td><strong>Newborn 0.25 μg/kg per min</strong></td>
<td>Δ10.3 ± 2.6</td>
</tr>
<tr>
<td><strong>Ewe 0.025 μg/kg per min</strong></td>
<td>Δ0.75 ± 0.18*</td>
</tr>
<tr>
<td><strong>Ewe 0.025 μg/kg per min</strong></td>
<td>Δ0.75 ± 0.18*</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE.

* P < 0.01. (Newborn compared to ewe, same dose.)
**Table 3** The Effects of Angiotensin II on Creatine Clearance, Urine Na, and K Excretion in the Newborn Lamb

<table>
<thead>
<tr>
<th></th>
<th>Creatinine clearance (ml/min)</th>
<th>Urine Na (total mEq)</th>
<th>Urine K (total mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Period 1</td>
<td>Period 2</td>
<td>Period 3</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>30-30</td>
<td>30-60</td>
</tr>
<tr>
<td>0.025 µg/kg per min</td>
<td>6</td>
<td>9.4 ± 3.7</td>
<td>7.3 ± 2.4</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>6</td>
<td>12.5 ± 3.1</td>
<td>10.3 ± 2.2</td>
</tr>
<tr>
<td>0.25 µg/kg per min</td>
<td>7</td>
<td>0.98 ± 0.24</td>
<td>0.88 ± 0.06</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>7</td>
<td>0.25 µg/kg per min</td>
<td>0.64 ± 0.13</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se.

* P < 0.05.

The functional renin-angiotensin system in the newborn (Siegel et al., 1974; Sulyok et al., 1979). One important purpose of the high renin-angiotensin-aldosterone levels would be to promote sodium reabsorption in the distal tubule and maintain a positive sodium balance in the newborn.

As shown in Figures 1 and 2 and Table 2, the change in response from baseline to peak for PRA and aldosterone in response to the 0.025 µg/kg per min and 0.25 µg/kg per min doses of angiotensin II was equal to the newborn lambs (groups 1 and 2). This suggests that renin inhibition and aldosterone stimulation by the low exogenous (0.025 µg/kg per min angiotensin II) dose may be above the plateau level of the dose-response curve. The renin inhibitory and aldosterone stimulatory secretion angiotensin II dose is lower than the pressor dose (Table 2).

It has been shown in the adult human and dog (Blair-West et al., 1971; McDonald et al., 1975; Roth et al., 1977) and in the newborn lamb (Siegel and Fisher, 1979) that angiotensin II inhibits renin secretion by negative feedback, and there is an increased renal renin content and renin release (Flamenbaum and Hamburger, 1974; Fray, 1978) at high angiotensin II levels. The long-term plasma angiotensin levels determine the ability of the adrenal to secrete aldosterone (Sealey et al., 1978). When angiotensin II levels are high, aldosterone secretion is augmented (Hallenberg et al., 1974; Oelkers et al., 1975). Therefore, the high endogenous levels of renin and angiotensin in the newborn lamb may be responsible for the greater renin inhibitory and aldosterone stimulatory responses seen in the newborn lamb compared to the non-activated renin-angiotensin system in the ewe (P < 0.01) (Figs. 1 and 2; Table 2).

Neither the low nor high dose of angiotensin II caused a significant decrease (period 2) in the GFR (Table 3). Angiotensin II has been shown to decrease GFR, renal blood flow, and cause an antinatriuresis and antidiuresis in sodium replete dogs (Fagard, 1978) with low renin-angiotensin levels; angiotensin II has been shown to cause no change in GFR, urine flow, and electrolyte excretion in sodium depleted dogs (Fagard, 1978) with high renin-angiotensin levels. Since the normal newborn has a low sodium intake with impaired sodium conservation and high renin-angiotensin levels, a maximal efferent and afferent arteriolar vasoconstriction may be present, and the addition of exogenous angiotensin produces no further effect. Although creatinine clearance is not an accurate measurement of GFR, it allows comparison of the 30-minute periods during the study.

The 0.25 µg/kg per min angiotensin II dose (Table 3) produced hypertension and a natriuresis (period 2) in the newborn lamb. During the development of hypertension caused by high renin levels, the differential effects of vasoactive substances on the glomerular arterioles cause an increase in capillary and peritubular pressures (Azar et al., 1974; Click et al., 1979) which may account for the pressure natriuresis. There also may be an internally controlled feedback to the renal tubules for the regulation of sodium balance which specifically in-
volves angiotensin (Thurau, 1974). The administration of a non-pressor (0.025 μg/kg per min) dose of angiotensin II to the newborn lamb produced no change in sodium excretion as in sodium-depleted dogs. Although these data suggest that the high endogenous plasma renin-angiotensin-aldosterone levels in the normal lamb are producing a maximal antinatriuresis, the acute increase in aldosterone may not have time to fully affect renal handling of sodium and potassium. Since the endocrine and renal systems appear to mature and function similarly in the newborn lamb and human, the effects found in the newborn lamb may be applicable to the human.

References

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