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Transplacental Transfer of Aldosterone and Its Effects on Renal Function in the Fetal Lamb

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Summary

Seven chronically catheterized fetal lambs between 100 and 130 days gestation (term, 140 to 145 days) and five newborn lambs were infused with *d*-aldosterone monoacetate, 100 μg/kg bolus, and 100 μg/kg over 60 min. Fetal lamb plasma aldosterone levels increased from a mean and S.E. baseline of 4.5 ± 0.3 μg/dl to >100 μg/dl. Maternal plasma aldosterone concentrations increased from 10.2 ± 0.8 to 26.2 ± 2.4 μg/dl after 15 min ($P < 0.05$) of the infusion. Amniotic fluid levels increased from 13.3 ± 0.8 to 23.8 ± 2.3 μg/dl ($P < 0.05$) after 15 min of the infusion. There was no change in plasma renin activity levels in the fetus or pregnant ewe. Urine sodium excretion decreased from 0.87 ± 0.09 to 0.34 total mEq ($P < 0.05$), and urine potassium increased from 0.25 ± 0.06 to 0.38 ± 0.07 total mEq ($P < 0.05$) between 60 and 90 min after the start of the infusion in the fetal lamb. There was no change in creatinine clearance or urinary sodium and potassium excretion in the newborn lamb. These data show that aldosterone crosses the placenta during the last trimester in the fetal lamb and can control sodium and potassium transport in the distal renal tubule. Lack of distal tubular responsiveness to aldosterone in the newborn is not due to maturational factors.

Speculation

Aldosterone can cross the placenta during the last trimester in the sheep, but the fetal adrenal cannot be stimulated. Sodium balance in the fetus is dependent on sodium balance in the mother.

Baseline plasma aldosterone concentrations are lower in the fetal lamb than in the pregnant ewe throughout gestation (12). Fetal adrenal aldosterone secretion cannot be stimulated by furosemide or hypertensive doses of angiotensin II (13) before parturition, suggesting that fetal aldosterone levels are maintained by the pregnant ewe. Pasqualini *et al.* (9) and Bayard *et al.* (1) have documented the placental transfer of aldosterone from mother to fetus in the guinea pig and human, respectively.

The distal renal tubular handling of sodium and potassium has been found unresponsive to exogenous aldosterone in the newborn human (5, 14). The purpose of this study is to determine in the sheep model: (1) whether aldosterone can cross the placenta from fetus to the mother; (2) whether aldosterone can inhibit plasma renin activity in the fetus and pregnant ewe; and (3) whether aldosterone can stimulate distal renal tubular reabsorption of sodium and increase potassium excretion in the fetal lamb.

MATERIALS AND METHODS

Seven chronically catheterized fetal lamb preparations between 100 and 130 days gestation (term, 140 and 145 days) were studied. Pregnant ewes were obtained from a local source and maintained in the vivarium before surgery. Rompun (0.1 to 0.2 ml), a tranquilizer, was administered to the ewe before uterotomy and fetal catherization; epidural anesthesia (5 ml of 2% xylocaine) was used for the surgical procedure. The uterus was exposed through a small midline abdominal incision, and the head was delivered through a small hysterotomy. Carotid arterial and jugular venous or femoral artery and vein, amniotic, and bladder polyvinyl catheters were placed. The fetus was returned to the uterine cavity, and the uterine incision was closed. The catheters were brought out through skin tunnels in the lateral abdominal wall and secured in a pouch attached to the back of the ewe. The animals were maintained on ampicillin for 5 days postoperatively and then studied.

Carotid arterial and jugular venous catheters were placed in the newborn under local anesthetic (xylocaine). The animal was returned to the mother and studied 4 to 5 days later. The newborn animals were restrained in a supine position on a specially constructed board so that they were nonstressed. They were kept warm and were quiet or asleep during the study. Blood gases and hemoglobin were measured before and after each study.

After a 30 min control period, d-aldosterone monoacetate was infused in the fetal and newborn lamb as a 100 μg/kg IV bolus followed by a 100 μg/kg over 60 min. Blood samples for plasma renin activity (PRA), plasma aldosterone, plasma sodium, and blood hematocrit were drawn 5 and 15 min before and 15, 50 and 80 min after the start of the infusion. 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 % 8-OH quinoline, 10 μl of 10 g % BAL, and 10 μl of 3 g % *O*-phenantroline were added to inhibit converting enzyme and angiotensinase. Twenty-five μl 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 equal aliquots, one aliquot for a blank (frozen) and the other aliqot for generation of angiotensin I at 37°C for one hr. PRA was measured by radioimmunoassay (6). Aldosterone, after column chromatography, was measured by radioimmunoassay (7). The coefficient of intra-assay variation was 8%, and inter-assay variation was 10%. Sodium was measured by flame photometer. Blood pressure was monitored continuously via pressure transducers and recorded on a Gould recorder. Statistics were measured by direct difference *t* test.

RESULTS

Table 1 shows that the fetal lamb plasma aldosterone levels increased to >100 μg/dl ($P < 0.001$) after the *d*-aldosterone monoacetate infusion. The pregnant ewe plasma aldosterone levels increased from 10.2 ± 0.8 μg/dl (mean ± S.E.) to 26.2 ± 2.4 after 15 min ($P < 0.05$) of the infusion. Amniotic fluid levels increased from a baseline of 13.3 ± 2.1 μg/dl to 23.8 ± 2.3 ($P < 0.05$) after 15 min of the infusion.

There was no change in plasma sodium hematocrit or mean aortic blood pressure (Table 2) in the fetus or pregnant ewe. There was no change in the hemoglobin or blood gases in the fetus

Table 3 shows that fetal, maternal, and amniotic PRA levels did not decrease after the *d*-aldosterone monoacetate infusion.

Table 4 shows the effects of *d*-aldosterone monoacetate on

Table 1. *The effect of exogenous aldosterone on aldosterone levels in the fetal lamb and ewe*

Plasma aldosterone (μg/dl)	*N* (7)	Control	Time (min) Postinfusion *d*-aldosterone monoacetate (100 μg/kg bolus plus 100 μg/kg over 60 min) 15	50	80
Fetal		4.2 ± 0.3[1]	>100 ± 0[2]	>100 ± 0	>100 ± 0
Maternal		10.2 ± 0.8	26.2 ± 2.4[3]	22.3 ± 2.1	13.9 ± 1.4
Amniotic		13.3 ± 2.1	23.8 ± 2.3[3]	43.8 ± 5.4	119 ± 8.5

[1] Mean ± S.E.
[2] $P < 0.001$.
[3] $P < 0.05$.

Table 2. *The effects of exogenous aldosterone on plasma sodium levels in the fetal lamb and ewe*

Plasma sodium (mEq/liter)	*N* (7)	Control	Time (min) Postinfusion *d*-aldosterone monoacetate (100 μg/kg bolus plus 100 μg/kg over 60 min) 15	50	80
Fetal		137 ± 1.25[1]	138 ± 1.3	137 ± 2.0	138 ± 2.1
Maternal		139 ± 1.23	140 ± 2.3	140 ± 2.5	140 ± 2.3

[1] Mean ± S.E.

Table 3. *The effect of exogenous aldosterone on PRA levels in the fetal lamb and ewe*

Plasma renin activity (μg/ml/hr)	*N* (7)	Control	Time (min) Postinfusion *d*-aldosterone monoacetate (100 μg/kg bolus plus 100 μg/kg over 60 min) 15	50	80
Fetal		3.1 ± 0.7[1]	2.7 ± 1.0	2.5 ± 1.5	3.3 ± 1.5
Maternal		1.7 ± 0.2	1.6 ± 0.3	2.2 ± 0.6	2.1 ± 0.5
Amniotic		1.2 ± 0.0	0.9 ± 0.0	0.7 ± 0.0	1.8 ± 0.2

[1] Mean ± S.E.

Table 4. *The effect of exogenous aldosterone on urinary excretion of sodium and potassium in the fetal lamb*

Creatinine clearance (ml/min)	*N*	Time (min) −30 (Period 1)	+30 (Period 2)	30–60 (Period 3)	60–90 (Period 4)
Fetus	7	2.55 ± 0.49[1]	2.67 ± 0.42	3.06 ± 1.21	2.84 ± 0.53
Urine sodium total mEq fetus	7	0.87 ± 0.09	0.81 ± 0.21	0.64 ± 0.15	0.34 ± 0.09[2]
Urine potassium total mEq fetus	7	0.25 ± 0.06	0.21 ± 0.06	0.33 ± 0.11	0.38 ± 0.07[2]

[1] Mean ± S.E.
[2] $P < 0.05$.

Table 5. *The effect of exogenous aldosterone on urinary excretion of sodium and potassium in the newborn lamb*

Creatinine clearance (ml/min)	*N*	Time (min) −30	+30	30–60	60–90
Newborn	5	13.0 ± 4.6[1]	12.2 ± 3.1	10.5 ± 2.1	11.1 ± 1.8
Urine sodium total mEq Newborn	5	0.11 ± 0.03	0.10 ± 0.01	0.08 ± 0.01	0.09 ± 0.01
Urine potassium total mEq Newborn	5	0.24 ± 0.04	0.20 ± 0.04	0.27 ± 0.12	0.27 ± 0.06

[1] Mean ± S.E.

glomerular filtration rate and tubular handling of sodium and potassium in the fetal lamb. There was no change in creatinine clearance. Urine sodium excretion decreased ($P < 0.05$) and potassium excretion increased ($P < 0.05$) between 60 and 90 min after the start of the infusion.

Table 5 shows the effects of *d*-aldosterone monoacetate on glomerular filtration rate and tubular handling of sodium and potassium in the newborn lamb. Plasma aldosterone levels increased from a baseline of 26.6 ± 6 μg/dl (mean ± S.E.) to >100 μg/dl. There was no change in creatinine clearance, urine sodium, or potassium excretion.

DISCUSSION

An infusion of bolus (100 μg/kg) and *d*-aldosterone monoacetate (100 μg/kg) to the fetus increased plasma aldosterone levels from a mean ± S.E. baseline of 4.5 ± 0.3 to >100 μg/dl (Table 1). Plasma aldosterone crossed the placenta from fetus to mother and increased maternal plasma aldosterone levels from 10.2 ± 0.8 to 26.2 ± 2.4 μg/dl ($P < 0.05$) after 15 min of the fetal infusion. Fetal plasma aldosterone crossed from fetus to amniotic fluid and increased aldosterone levels from a mean ± S.E. baseline of 13.3 ± 2.1 to 23.8 ± 2.3 μg/dl after 15 min of the infusion. Placental transfer (9) of aldosterone from mother to fetus has been shown in the guinea pig. Plasma aldosterone levels are higher in the pregnant ewe than in the fetal lamb from 100 days gestation (12) to term, and the fetal aldosterone levels increase concommitantly with maternal levels after 125 days gestation (12). Fetal lamb adrenal aldosterone cannot be stimulated before term. This shows that aldosterone transfers from fetal lamb to pregnant ewe and suggests transplacental transfer from mother to fetus. If the human fetal and maternal relationships are similar, the passage of aldosterone, sodium, and water (8) across the placenta would allow the pregnant mother to maintain fetal salt balance.

Bayard *et al.* (1) demonstrated that aldosterone crossed the placenta in the human at the time of cesarian section and the fetal levels were 2 to 12 times higher than the maternal levels, showing that the human fetus secreted aldosterone at the time of birth. Beitins *et al.* (2) found that infants of mothers on a low sodium diet or diuretic medication had higher cord blood and postnatal plasma aldosterone concentrations than did control infants, suggesting that aldosterone can be stimulated during parturition.

There was no change in the PRA (Table 3) in the fetus, pregnant ewe, or amniotic fluid during the 90-min study period. A possible direct action of aldosterone on renin secretion was studied by Geelhoed and Vander (3) with negative results; they found that renin release failed to decrease if increased body fluid volume was prevented by sodium restriction. Robb *et al.* (10) suggested that DCA depressed PRA either by expansion of the extracellular fluid volume or by an increase in total body sodium. The data in Table 3 show that there was no direct inhibition of PRA in the fetus or pregnant ewe; because the study period was too short to provide an increase in extracellular fluid volume or an increase in total body sodium, indirect suppression could not be evaluated.

Aldosterone does not have vasoconstrictor or vasodilator properties in the adult. Aldosterone did not change mean arterial blood pressure or glomerular filtration rate in the fetus (Table 4). Renal blood flow needs to be measured to determine whether aldosterone has any hemodynamic effect in the fetus. Aldosterone regulates sodium and potassium balance by acting directly on the distal renal tubule to stimulate the active process which accounts for the transfer of sodium from the glomerular filtrate to the interstitial compartment of the kidney, effecting the retention of sodium and chloride ions in exchange for potassium and hydrogen ions (4). During the last trimester between 100 and 130 days gestation, there was fetal distal renal tubular responsiveness to aldosterone (Table 4). Urine sodium decreased from a mean ± S.E. of 0.87 ± 0.09 total mEq in the control period to 0.34 ± 0.09 total mEq ($P < 0.05$) between 60 and 90 min after the start of the aldosterone infusion. Urine potassium increased from a mean ± S.E. of 0.25 ± 0.06 to 0.38 ± 0.07 total mEq ($P < 0.05$) between 60 and 90 min. The inability to stimulate fetal adrenal aldosterone secretion would inhibit the availability of the hormone to conserve distal renal sodium and excrete potassium. This may contribute to the 5 to 10% fractional excretion of sodium and natriuresis that occurs in the fetal lamb *in utero* (11).

The distal tubular handling of sodium and potassium has been unresponsive to exogenous aldosterone in the newborn human (5, 14). This unresponsiveness was confirmed in the newborn lamb (Table 5) in spite of achieving similarly high plasma aldosterone levels, >100 μg/dl. Inasmuch as there is distal tubular responsiveness to aldosterone in the fetal lamb, a factor or factors other than maturation of receptor and transport mechanisms is responsible in the newborn. The endogenous aldosterone levels are higher in the newborn than the fetus (26 compared to 8 μg/dl, respectively) which may result in maximal reabsorption of sodium and excretion of potassium and unresponsiveness to exogenous aldosterone under basal conditions.

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