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Renal Metabolism in Fetal and Newborn Sheep

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ABSTRACT. The substrate and oxygen uptake by some organs in intact developing animals has been described, however, the kidney has not been studied. To examine substrate and oxygen uptake by the kidney, we implanted polyvinyl catheters into the renal vein, descending aorta, inferior vena cava, and urinary bladder of 11 fetal sheep (120–125 days gestation) and eight newborn lambs (1 day postnatal). Four days after surgery, blood samples were obtained simultaneously from the renal vein, aorta, and inferior vena cava for determination of oxygen content and saturation, and glucose and lactate concentrations. Renal blood flow was determined by the radionuclide-labeled microsphere method in the fetal lambs and by measuring ^{14}C-inulin clearance in the newborn lambs. The fetal and newborn kidneys consumed oxygen at rates of 123 ± 16 and 785 ± 79 μmol/min/100 g kidney weight (mean ± SEM), respectively. The increase in oxygen consumption from the fetal to the newborn period was accompanied by an increase in oxygen extraction from 25–35%, a large increase in oxygen delivery from 418 ± 38 to 2231 ± 127 μmol/min/100 g, and marked increases in glomerular filtration rate and sodium reabsorption (measured in six additional fetal sheep and the eight newborn lambs). This suggests that the postnatal increase in renal tubular activity is associated with an increase in oxygen consumption. Lactate was taken up by both fetal and newborn kidneys, and in nine of the 11 fetuses and in four of the eight newborns, there was net glucose release from the kidney. (*Pediatr Res* 19: 641–644, 1985)

Abbreviations

A-V, arteriovenous
$\dot{V}O_2$, oxygen consumption
GFR, glomerular filtration rate

The transition from pre- to postnatal life is associated with a marked increase in oxygen consumption in the sheep (1). Most of this change is related to an increase in metabolism for maintenance of body temperature and ventilation. However, myocardial oxygen consumption also increases in response to the demands of increases in heart rate, arterial pressure, and peripheral vascular resistance (2, 3). After the placenta is removed from the circulation, the kidney must assume fluid regulatory and excretory functions. To achieve the increase in renal function, it might be expected that renal consumption of oxygen and substrates increases after birth. Changes in the plasma concentration of oxygen and metabolic substrates, such as glucose and lactate, and in renal blood flow that occur after birth influence substrate delivery rates to the kidney and also may alter renal metabolism. To examine renal metabolism and oxygen consumption we have developed a method of sampling renal venous blood in chronically maintained preparations of sheep (4), and have used this method to measure arteriovenous concentration differences of oxygen and various potential substrates of renal metabolism in fetal and newborn sheep. In conjunction with measuring renal blood flow, we calculated the rates of renal uptake and release of these substances.

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MATERIALS AND METHODS

Seventeen fetal sheep (119–133 days gestation) and eight newborn lambs (5–6 days old) were studied. For the fetal sheep study, pregnant ewes were fasted for 24–48 h prior to surgery. After local anesthesia with lidocaine HCl (2 ml of 2%), low epidural or spinal anesthesia was induced in the ewe with 4 ml of 1% tetracaine hydrochloride (Pontocaine hydrochloride, Breon Laboratories, New York, NY). The ewes were placed in a supine position and polyvinyl catheters (1.3 mm id, 2.3 mm od) were inserted into the left maternal dorsalis pedis artery and vein and passed centrally to lie in the inferior vena cava and descending aorta. Ten percent dextrose in 0.9% saline was infused intravenously and 50–100 mg of ketamine hydrochloride (Vetalar, Parke-Davis, Morris Plains, NJ) was administered to the ewe during surgery every 15–20 min.

Through a ventral midline abdominal incision, the pregnant horn of the uterus was palpated. The fetal hind portion was exteriorized through an 8–10 cm incision in the uterus. Under local anesthesia, polyvinyl catheters (0.8 mm id, 1.2 mm od) were inserted into hindlimb arteries and veins and advanced to the descending aorta and inferior vena cava. A silicone-rubber catheter with multiple side-holes was inserted into the urinary bladder through a suprapubic incision as previously described (4). The fetal skin was incised 4–8 cm from the base of the 12th rib parallel with and anterior to the spine; through this incision the renal vein was exposed and a modified Teflon-polyvinyl catheter was inserted into the vein and secured with a 6–0 silk suture as described previously (4). All fetal incisions were sutured and the fetus was returned to the uterus. An additional polyvinyl catheter was inserted into the amniotic cavity. All fetal vascular catheters were filled with heparin sodium solution and sealed. The uterus and maternal abdomen were sutured in layers. Antibiotics (600 mg kanamycin and 1 million U penicillin) were administered intravenously to the ewe and instilled into the amniotic cavity postoperatively and each day thereafter. At least 4 days elapsed between the surgery and experiment.

For the newborn lamb study, 1-day-old lambs were sedated with a subcutaneous injection of ketamine hydrochloride (5 mg/kg). Additional ketamine was administered intravenously during

surgery as needed. Using local anesthesia with 1% lidocaine HCl, we placed polyvinyl catheters (1.0 mm id, 1.8 mm od) into the dorsalis pedis arteries and veins and passed them centrally. As in the fetus, a silicone-rubber catheter was placed into the urinary bladder through a ventral abdominal incision. A Teflon-polyvinyl catheter was inserted into the left renal vein via a retroperitoneal incision. To prevent the renal venous catheter from being dislodged, the free end of the catheter was looped subcutaneously and the skin incision was sutured. After surgery was completed, antibiotics (1 g ampicillin and 10 mg/kg gentamycin) were administered intravenously. Studies were performed after at least 4 days of recovery.

The fetuses were studied while the ewe stood quietly in a study cage. Fetal pressures and heart rate were monitored continuously with Statham P23Db pressure transducers and a cardiotachometer triggered by the arterial pressure pulse, and recorded on a Beckman 8-channel Dynograph direct-writing recorder. Metabolic and renal function measurements were made in two groups of fetuses because the amount of blood that can be obtained from each fetus is limited. Metabolic measurements were made in 11 fetal sheep (123–133 days gestational age); blood samples were obtained simultaneously from the descending aorta and renal vein for determination of pH, blood gases, oxygen content, glucose, and lactate concentrations. We determined renal blood flow by injecting 15-μm diameter radionuclide-labeled microwere obtained simultaneously from the descending aorta and ^{95}Nb, ^{54}Mn, or ^{65}Zn) into the inferior vena cava while obtaining a reference sample from the descending aorta (5). Renal function was measured in six fetal sheep (119–126 days gestational age) as follows. A priming dose of ^{14}C-inulin (5–15 mCi/mmol, Amersham Corp., Arlington Heights, IL) dissolved in 5% dextrose in 0.20% NaCl was injected (10 μCi/kg) and an infusion (0.1 μCi/min/kg) was initiated at least 1 h prior to blood sampling. Urine was collected for four 20-min periods and blood was sampled at the midpoint of each urine collection period in order to determine pH and blood gases, Na concentration, and ^{14}C-radioactivity in arterial plasma and urine. Metabolic and renal function measurements were made in the eight newborn lambs while they were quietly supported in a sling. ^{14}C-inulin was administered and urine was collected as described for the fetal sheep study. At the midpoint of each urine collection period, blood samples were obtained simultaneously from the descending aorta and renal vein for the determination of pH, blood gases, O_2 content, ^{14}C-radioactivity, glucose, lactate, β-hydroxybutyrate, and α-amino nitrogen concentrations. We determined renal blood flow by measuring renal extraction of ^{14}C-inulin and applying the Fick principle and Wolf's equation (6). Blood flow measured by this method is generally 10–15% higher than that measured by the microsphere method (7) (Iwamoto HS, unpublished observations).

Glucose concentrations in whole blood were determined on blood samples that were immediately chilled, precipitated in $Ba(OH)_2$ and $ZnSO_4$, and centrifuged. The extracts were stored at −20° C until assay; we used a commercially available kit based on the glucose oxidase and peroxidase method (Sigma, St. Louis, MO). Lactate and β-hydroxybutyrate concentrations in whole blood were determined on blood samples that were immediately chilled, precipitated with perchloric acid, and centrifuged. The extracts were stored at −20° C; we assayed lactic acid using lactate dehydrogenase (Sigma), and β-hydroxybutyrate using β-dehydrogenase after the extracts were neutralized (modification of Reference 8). α-Amino nitrogen concentrations in plasma were determined by a method based on production of stable trinitrophenol derivatives (Barnes N, Nishino V, personal communication). P_{O_2}, pH, and P_{CO_2} were determined with a Corning Model 165 or 175 blood gas analyzer (Corning Medical, Medfield, MA). We estimated oxygen contents in fetal blood (ml O_2/dl blood) by multiplying the hemoglobin concentration by the fractional saturation of the blood and 1.35 ml O_2/g hemoglobin. Oxygen contents in newborn blood were determined by use of a Lex-O_2-Con (Lexington Instruments Corp., Waltham, MA). To obtain values with units of mM, oxygen contents (ml O_2/dl) were divided by 22.4 ml O_2/mmol and multiplied by 10. Fetal values are an average of two determinations. In the newborns, renal blood flow and A-V oxygen content were measured during each of the four clearance periods. We calculated four values of oxygen consumption by multiplying each renal blood flow value by the simultaneously obtained A-V oxygen content. Thus, the numbers reported in Table 2 are the average of four values and may not equal average renal blood flow times average A-V oxygen content (also reported in Table 2). Substrate fluxes were calculated in a similar manner. Plasma and urine sodium concentrations were determined by flame photometry (Instrumentation Laboratory, Inc., Lexington, MA; Beckman Instruments, Fullerton, CA). ^{14}C-radioactivity was measured by liquid scintillation. GFR was calculated as urine cpm × urine flow rate divided by arterial cpm. Renal sodium filtration rate was calculated as the product of arterial plasma sodium concentration and GFR. Sodium excretion rate was calculated as the product of urine sodium concentration and urine flow rate. Renal sodium reabsorption rate was calculated as filtration rate minus excretion rate. Statistical differences between fetal and newborn values were assessed by an unpaired *t* test or Mann-Whitney U test.

RESULTS

All animals included in these studies were in good health with total body and kidney weights, arterial pH, and blood gas values within the expected range (Table 1).

Renal blood flow and arterial oxygen content were greater in newborn than in fetal lambs (Table 2). Oxygen delivery to the kidney, calculated as arterial oxygen content times renal blood flow, was 2221 ± 204 μmol/min/100 g in the newborns and 496 ± 77 in the fetuses (significantly different values, $p < 0.001$). In addition to the higher oxygen delivery rate to the newborn kidney, oxygen extraction by the newborn kidney was also greater (35 *versus* 25% for the newborn *versus* fetal sheep, $p < 0.05$). Consequently, the amount of oxygen consumed by the newborn kidney was much greater than that consumed by the fetal kidney.

The GFR in newborn sheep was more than six times that in fetal sheep (Table 3). Sodium filtration rate was greater and sodium excretion rate was less in newborn sheep. In addition, the actual and fractional amount of sodium reabsorbed by the newborn kidney was significantly greater than that reabsorbed by the fetal kidney.

Arterial glucose concentrations were greater in the newborn than in the fetal sheep (Table 4). In nine of 11 fetuses and in four of eight newborn sheep arteriovenous concentration difference was negative for glucose across the kidney indicating that the kidney produced glucose. Arterial lactate concentrations in the fetuses (1.42 ± 0.12 mM) were significantly greater than in the newborns (0.87 ± 0.04 mM, $p < 0.01$) (Fig. 1). Arteriovenous difference for lactate was consistently positive across the fetal (0.12 ± 0.02 mM) and newborn (0.06 ± 0.08 mM) renal circulations indicating net lactate uptake. There was no net flux of α-amino nitrogen, but there was net uptake of β-hydroxybutyrate by the newborn kidney (Fig. 2) at a rate (19.6 ± 2.8 μmol/min/100 g) which could account for 13 ± 2% of the oxidative metabolic rate.

Table 1. *Total body and kidney wt, and pH, P_{O_2}, P_{CO_2} of arterial blood in fetal and newborn sheep (mean ± SEM)*

	Fetus	Newborn
n	17	8
Body wt (kg)	2.90 ± 0.12	5.21 ± 0.47*
Kidney wt (g)	28.8 ± 1.30	40.2 ± 1.39*
pH	7.36 ± 0.01	7.34 ± 0.01*
P_{O_2} (torr)	21 ± 0.5	95 ± 2.4*
P_{CO_2} (torr)	52 ± 1.0	34 ± 1.1*

* $p < 0.05$, significantly different from fetal values.

Table 2. *Renal blood flow, oxygen content, and oxygen consumption in fetal and newborn sheep*

	Blood flow (ml/min)		O_2 content mM*		Oxygen consumption (μmol/min)	
n		per 100 g	A	A-V		per 100 g
Fetus						
1	52.4	148	2.67	0.63	33.16	94
2	35.0	131	3.40	0.60	21.02	79
3	55.5	203	2.86	0.79	43.86	160
4	44.7	163	3.16	0.76	33.94	124
5	34.9	150	2.33	0.83	29.00	125
6	45.7	192	2.79	0.59	26.99	113
7	29.7	139	1.68	0.54	16.02	75
8	46.9	135	3.13	0.68	31.9	92
9	51.3	121	2.37	0.60	30.8	73
10	81.4	356	3.23	0.68	55.3	242
11	67.6	222	2.44	0.77	52.4	171
Mean	49.55	178	2.73	0.68	34.04	123
SEM	4.75	21	0.16	0.03	3.83	16
Newborn						
1	176	464	5.62	2.59	478	1265
2	153	358	5.27	1.97	297	698
3	183	408	6.04	1.45	274	612
4	190	475	5.32	2.41	473	1181
5	150	331	3.81	1.94	404	668
6	112	278	6.18	1.36	154	384
7	161	465	5.30	1.56	247	715
8	161	448	6.34	1.70	272	755
Mean	161†	403†	5.49†	1.87†	325†	785†
SEM	9	28	0.301	0.168	44	111

* A is concentration in descending aorta; A-V is concentration difference between descending aorta and renal vein.

† $p < 0.001$, significantly different from fetal value.

Table 3. *Sodium handling by fetal and newborn sheep kidneys (mean ± SEM)*

	Fetus	Newborn
n	6	8
GFR (ml/min)	2.43 ± 0.11	15.93 ± 5.93*
Filtration (μEq/min)	361 ± 16	2294 ± 394*
Reabsorption (μEq/min)	337 ± 18	2291 ± 395*
Excretion (μEq/min)	23 ± 4	3.5 ± 1.2*
Reabsorption (%)	93.4 ± 1.3	99.8 ± 0.1*

* $p < 0.005$, significantly different from fetal value.

DISCUSSION

Among the important changes that occur at birth are the removal of the placenta from the circulation and the assumption by the kidney of fluid regulatory and excretory functions. Renal blood flow increases from 3–4% of combined ventricular output in fetal lambs (9) to 8–10% of cardiac output in newborn lambs (10, 11). We have confirmed that the kidney of newborn lambs receives three to four times more blood flow than the fetal kidneys in relation to renal mass, and have shown that oxygen consumption by the newborn kidney increases markedly as compared with the fetal kidney.

We have determined that the rate of $\dot{V}O_2$ by the fetal sheep kidney at 123–133 days gestation is 123 ± 16 μmol/min/100 g. Assuming that the fetuses in this study consumed oxygen at a rate previously reported for fetal sheep (19), the kidneys account for 3–4% of total $\dot{V}O_2$. This rate is comparable with the $\dot{V}O_2$ of the fetal gastrointestinal tract reported by Edelstone and Holzman (12) but less than that of the fetal brain (13), heart (2), and liver (14). We also determined that the $\dot{V}O_2$ of the newborn kidney is approximately six times that of the fetal kidney and greater than that of the newborn heart (3), brain (15), and liver (16). The increase in renal $\dot{V}O_2$ after birth probably reflects the increase in renal function after birth. In addition, GFR and

Table 4. *Glucose concentration and flux in fetal and newborn sheep*

	Glucose mM*		Glucose flux (μmol/min)	
	A	A-V		per 100 g
Fetus				
1	0.687	0.012	0.629	1.77
2	1.249	−0.105	−3.68	−13.76
3	0.934	−0.015	−0.833	−3.04
4	0.968	−0.029	−1.30	−4.73
5	0.577	−0.004	−0.140	−0.601
6	1.415	−0.041	−1.88	−7.86
7	0.749	−0.018	−0.534	−2.50
8	0.938	−0.017	−0.797	−2.30
9	1.12	0.00	0.00	0.00
10	0.898	−0.014	−1.139	−4.984
11	0.918	−0.088	−5.949	−19.54
Mean	0.950	−0.029	−1.420	−5.231
SEM	0.077	0.012	0.594	2.008
Newborn				
1	5.67	0.015	0.660	1.74
2	5.75	−0.058	−6.50	−15.15
3	6.16	−0.410	−70.70	−158
4	7.84	−0.400	−150	−376
5	6.35	−0.165	−20.38	−45
6	4.92	0.101	8.87	22.3
7	4.76	0.014	1.04	5.30
8	6.56	0.111	17.12	47.61
Mean	6.001†	−0.099	−27.5	−64.7
SEM	0.370	0.079	21.3	53

* A is concentration in descending aorta; A-V is concentration difference between descending aorta and renal vein. Glucose flux was calculated in a manner similar to oxygen consumption.

† $p < 0.001$, significantly different from fetal value.

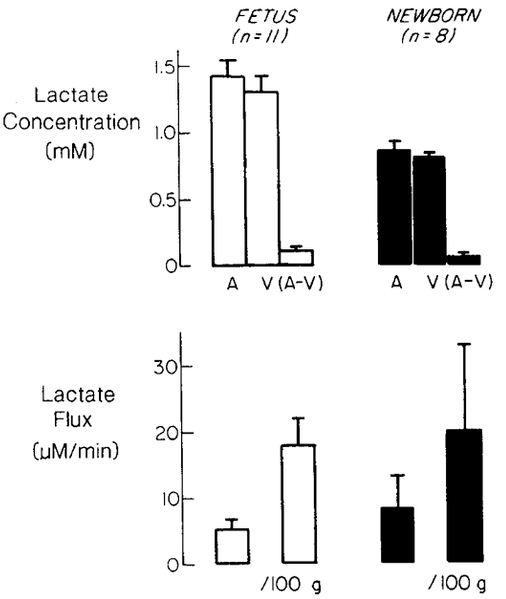

Fig. 1. Arterial, renal venous, and A-V concentrations of lactate in fetal and newborn sheep. Lactate flux was calculated in same manner as glucose flux. (*A-V*) in newborns and (*A-V*) and lactate flux in fetuses were significantly greater than zero, ($p < 0.05$).

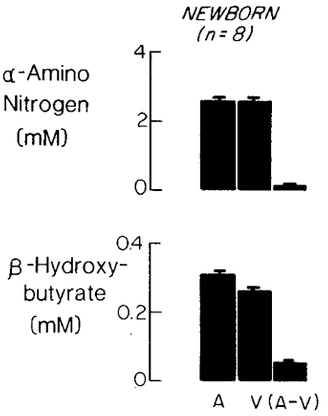

Fig. 2. Concentrations of α-amino nitrogen and β-hydroxybutyrate in newborn lambs. (A-V) for β-hydroxybutyrate was significantly greater than zero ($p < 0.001$), paired t test.

sodium fitration rate are more than six times as great in newborn than in fetal sheep; our values are not significantly different from those previously reported (17, 18). The actual rate and fraction of the filtered sodium that was reabsorbed were also greater in newborn sheep. Since sodium reabsorption represents a major portion of renal tubular activity, this increase in sodium reabsorption requires an increase in metabolic activity, which probably accounts for the greater oxygen consumption rate by the newborn relative to the fetal kidney. A similar correlation between sodium reabsorption and oxygen consumption has been presented by Elinder and Aperia (7) in studies of neonatal rats.

The substrate-oxygen quotient is an expression of the proportion of total oxygen uptake that could be accounted for if a substrate is completely oxidized to CO_2 and H_2O (19). We calculated substrate-oxygen quotients and found that, in the newborn kidney, lactate uptake could account for 16 ± 5% and β-hydroxybutyrate uptake could account for 13 ± 2% of the oxidative metabolic requirement. In the fetal kidney, lactate uptake could account for 54 ± 11% of the metabolic requirement. We were thus unable to account for the total substrate requirements of the developing kidney although we have not yet examined every potential substrate of metabolism. The kidneys may consume glucose derived from glycogen in the kidney, but this cannot be determined only by measuring net substrate fluxes across the renal vascular bed.

In nearly every fetus and in half the newborns studied A-V concentration difference for glucose was consistently positive across the renal circulation, indicating net release of glucose from the kidney. The glucose may have derived from glycogen breakdown or gluconeogenesis. The kidneys of developing lambs are known to store glycogen (20). The enzymes necessary to produce glucose from other substrates are present during the last trimester of gestation (21). Previous studies of total glucose turnover have not been able to demonstrate significant gluconeogenesis from either lactate or alanine (22); since the net glucose production by the kidney is a small percentage of total glucose turnover, it may not be possible to detect it. Renal gluconeogenesis has been reported to occur in the neonatal baboon and adult sheep (23, 24); in preliminary studies we have demonstrated renal gluconeogenesis from ^{14}C-lactate in fetal lambs late in gestation (Gleason CA, Iwamoto HS, Rudolph AM, unpublished observations). In the present study, lactate taken up by the kidney could have been utilized directly or could have been directly converted to glucose and released or first deposited as glycogen then released as glucose, as has been shown to occur in adult rats (25, 26). The glucose released may be used by the rest of the body or by the kidney itself. The small net glucose produced by the kidney may not represent total gluconeogenesis because the kidney may utilize some of the glucose produced for its own metabolism. Further studies are required to confirm this notion.

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