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Tissue glucose and lactate metabolism and interconversions in pregnant and lactating sheep

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1. Continuous infusions of [^{14}C]glucose and [^{14}C]lactate on separate days, and measurements of blood flow-rate, were used to obtain values for rates of unidirectional metabolism and of interconversion of glucose and lactate in the portal-drained viscera, liver and hind-quarters of ewes during late pregnancy and early lactation. All infusions were made within 5 h after the morning meal, when steady-state conditions appeared to exist.

2. Use was made of ewes that had been appropriately catheterized during pregnancy, and whose catheters remained patent through into lactation.

3. The liver was the main source of glucose production (67–70%) during both pregnancy and lactation. Other sources were the portal-drained viscera (absorbed glucose) and, presumably, the kidneys. Over 80% of the glucose was utilized by the peripheral tissues with approximately 35–40% of utilization being attributable to the hind-quarters.

4. Of the total lactate production, 76% occurred in the peripheral tissues during pregnancy but only 36% during lactation. While the liver utilized 73% of lactate during pregnancy, this value fell to only 42% during lactation, at which time the portal-drained viscera utilized 26% of the lactate.

5. During pregnancy, approximately 80% of the lactate arose from glucose, chiefly in peripheral tissues, while at least 12% of the glucose arose from lactate, chiefly in the liver. During lactation the extent of these interconversions was decreased.

6. Despite the interconversions, whole-body turnover rates for glucose and lactate were under- or overestimated by only 4–10% and 2–5% respectively. Furthermore, a comparison of turnover rates obtained with [U-^{14}C]- and [6-^{3}H]glucose indicated that there was only 6 and 2% recycling of glucose-C during pregnancy and lactation respectively.

7. Under the conditions employed in this study, lactate does not appear to be a major precursor of glucose in the ruminant, and most of the lactate taken up by the liver must be used for purposes other than gluconeogenesis, such as oxidation or alternative anabolic pathways.

It is known that gluconeogenesis provides most of the glucose required by ruminants (Lindsay, 1970; Bergman *et al.* 1974). Although the contribution to gluconeogenesis of precursors such as propionate (Bergman *et al.* 1966; Judson *et al.* 1968; Corse & Elliot, 1970), glycerol (Bergman *et al.* 1968) and key amino acids (Wolff & Bergman, 1972; Brockman & Bergman, 1975; Heitmann & Bergman, 1981) has been studied in sheep, only little is known about the sparing effect of the Cori and alanine cycles in which lactate, pyruvate and alanine are recycled back to glucose. While total recycling of glucose-carbon in the whole body may be inferred from infusions of dual-labelled [U-^{14}C]- and [6-^{3}H]glucose (Judson & Leng, 1972; Brockman *et al.* 1975; Wilson *et al.* 1981), no values have been directly obtained for specific tissues. Thus, rates of production and utilization of lactate by specific ruminant organ systems remain largely unexplored (Baird *et al.* 1980).

Rates of unidirectional utilization and production, and interconversions, of glucose and lactate were therefore determined in the portal-drained viscera, liver and hind-quarters of the sheep described by Baird *et al.* (1983). Use was made of the mathematical model described previously for amino acids (Wolff & Bergman, 1972; Heitmann & Bergman, 1981).

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METHODS

Animals

The sheep, diets and method of feeding have been described by Baird *et al.* (1983). Briefly, all animals were fed to requirement (Ministry of Agriculture, Fisheries and Food, 1975) with one-third of the energy intake as Lucerne (*Medicago sativa*) hay and two thirds as roughage–concentrate pellet. Polyvinyl catheters were implanted in the hepatic, portal and mesenteric veins, as well as the caudal vena cava and aorta, between 19 and 49 d prepartum (Katz & Bergman, 1969*a*). Animals were not used for experiment until at least 2 weeks after this operation. On the day before an experiment, a temporary catheter was also inserted, for infusion purposes, into a jugular vein. The catheters were filled with sterile heparinized physiological saline (9 g sodium chloride/l; 100 units heparin/ml) and flushed twice weekly.

Experimental design and procedure

As described previously (Baird *et al.* 1983), a total of eight experiments were conducted on four sheep, five experiments during pregnancy and three during lactation. Each experiment consisted of a primed infusion, via the jugular catheter, of D-[U-^{14}C]glucose + D-[6-^{3}H]glucose (approximately 15 and 21 μCi/h respectively) followed 2–3 d later by a primed infusion of L-[U-^{14}C]lactate (approximately 9 μCi/h). Infusions began about 30 min after the morning feed had been given and lasted for 4·5 h, i.e. from approximately 08.30 to 13.00 hours. The infusion rate was 46·3 ml/h and infusions were started with a priming dose of 60 ml of infusate. A solution of *p*-aminohippuric acid (15 g/l; PAH) in sterile saline was also infused via the mesenteric catheter for the last 2·5 h of the isotope infusion. This was done to estimate blood flow through the portal-drained viscera and liver (Katz & Bergman, 1969*b*).

Four sets of simultaneously withdrawn blood samples (each sample being 21 ml) were obtained from the portal and hepatic veins, caudal vena cava and aorta at 0·5 h intervals from 3 to 4·5 h after the start of infusion. Each blood sample was analysed for both specific activity and concentrations of glucose and lactate and concentrations of pyruvate and alanine. The concentration of PAH was measured only in the hepatic, portal and arterial samples. Mean values were obtained for the four samples from each blood vessel.

Chemical methods

The blood concentrations and specific activities of glucose and lactate were determined as described previously (Baird *et al.* 1983), as were the concentrations of pyruvate and alanine. PAH concentrations were analysed as previously described (Katz & Bergman, 1969*b*) but by using an automated system (Technicon Instruments Corp., Tarrytown, NY).

Calculations

Whole blood flow rates through the portal-drained viscera and liver were calculated from the down-stream dilution of PAH as previously described (Katz & Bergman, 1969*b*). Hepatic arterial flow was obtained from the difference between hepatic flow and portal flow. Blood flow through the hind-quarters was assumed to be 1·5 l/min. This was the mean rate obtained previously in either fed or fasted animals (Heitmann & Bergman, 1981). Some mammary venous blood, however, could drain into the vena cava during lactation and thus increase this rate of hind-quarter blood flow. The precise amount is unknown, but it could possibly amount to as much as 20% of the total. The net production or removal of glucose and lactate by each of the above tissues was then calculated by multiplying the venoarterial blood concentration differences by the rate of blood flow. A positive value thus indicates production whereas a negative value indicates utilization.

For calculation of unidirectional utilization and production, and interconversions, across individual tissues, the specific activities of both the inflowing (arterial) precursor and outflowing (venous) product must be measured. Calculations of utilization and production of blood glucose and lactate by the portal-drained viscera, liver and hind-quarters thus followed the procedures described previously for amino acids (Wolff & Bergman, 1972; Brockman & Bergman, 1975; Heitmann & Bergman, 1981). In brief, unidirectional utilization of glucose or lactate by the tissue in question was calculated by multiplying the fraction of [^{14}C]glucose or [^{14}C]lactate that was removed by the total blood glucose or lactate that was flowing into the tissue. Unidirectional production was the addition of unlabelled glucose or lactate to the venous blood and was calculated by adding the unidirectional utilization to the net production.

Unidirectional rates of glucose were further broken down into that portion of the glucose utilized that was converted into lactate and that portion of the glucose produced that was derived from lactate. Similarly, lactate unidirectional rates were subdivided into those portions converted into, or derived from, glucose. The equations used to calculate these rates of glucose–lactate interconversions are again the same as those published earlier for amino acids (Wolff & Bergman, 1972; Heitmann & Bergman, 1981) and were calculated for each tissue in a given animal when [^{14}C]glucose and [^{14}C]lactate were infused in separate experiments. The actual quantity of glucose derived from lactate in the liver must, however, be regarded as the minimal glucogenic potential of lactate. This is because of the inevitable crossover of ^{14}C and ^{12}C at the level of oxaloacetate (Krebs *et al.* 1966). The model is illustrated in Fig. 1 (p. 276) and its solution was obtained by the use of six simultaneous equations. For the portal-drained viscera, they are as follows:

$$ {}^{glu}S_a{}^{glu} \cdot F_p + {}^{glu}SA_a{}^{lac} \cdot R_8 = {}^{glu}SA_a{}^{glu} \cdot (R_2 + R_3) + {}^{glu}S_p{}^{glu} \cdot F_p \quad (1) $$

$$ {}^{lac}S_a{}^{glu} \cdot F_p + {}^{lac}SA_a{}^{lac} \cdot R_8 = {}^{lac}SA_a{}^{glu} \cdot (R_2 + R_3) + {}^{lac}S_p{}^{glu} \cdot F_p \quad (2) $$

$$ {}^{lac}S_a{}^{lac} \cdot F_p + {}^{lac}SA_a{}^{glu} \cdot R_3 = {}^{lac}SA_a{}^{lac} \cdot (R_7 + R_8) + {}^{lac}S_p{}^{lac} \cdot F_p \quad (3) $$

$$ {}^{glu}S_a{}^{lac} \cdot F_p + {}^{glu}SA_a{}^{glu} \cdot R_3 = {}^{glu}SA_a{}^{lac} \cdot (R_7 + R_8) + {}^{glu}S_p{}^{lac} \cdot F_p \quad (4) $$

$$ R_1 + R_4 + R_8 = R_2 + R_3 + R_5 \quad (5) $$

$$ R_3 + R_6 + R_9 = R_7 + R_8 + R_{10} \quad (6) $$

where ${}^{lac}S_a{}^{glu}$ and ${}^{lac}S_p{}^{glu}$ are the [^{14}C]glucose activities (μCi/l) in arterial and portal blood respectively, when [^{14}C]lactate was infused, ${}^{lac}SA_a{}^{glu}$ is the specific activity (μCi/mg atom C) of glucose in arterial blood when [^{14}C]lactate was infused, etc. and F_p is the portal blood flow (l/h). R_1, R_2, R_3, etc. are the fluxes of metabolite C (mg atoms C/h) as shown in Fig. 1. For total peripheral tissues, no values could be assigned to R_1, R_5, R_6 and R_{10}, because blood flow was not known, but the differences, $R_1 - R_5$ and $R_6 - R_{10}$ (net peripheral uptake) were equated with net splanchnic output. Similarly, peripheral utilization of the glucose- or lactate-^{14}C (μCi/h) was equal to the infusion rate minus total splanchnic uptake of ^{14}C (cf. Wolff & Bergman, 1972). This model measures only irreversible utilization and *de novo* production, i.e. from non-^{14}C sources. It will not measure so-called futile cycles, such as lactate to pyruvate, alanine, etc., and again back to lactate.

Apparent turnover rates of glucose and lactate were calculated as described by Baird *et al.* (1983), although it must be recognized that lactate turnover is probably underestimated by 10–15% (Baird *et al.* 1983). Turnover rates of both glucose and lactate were, however, corrected for newly absorbed, unlabelled metabolite that was immediately removed by the liver from the portal blood (Brockman & Bergman, 1975). The equation is: corrected turnover = (apparent turnover) + (portal production × fractional uptake of ^{14}C metabolite by liver).

Statistics. Statistical analyses were carried out as described by Baird *et al.* (1983).

Table 1. *Regression analysis of change in the values for blood flow rate with time during sampling in the ewes*

Infusate	Blood flow	Physiological status	Blood flow rate (l/min) Mean	SE	Slope of regression line (change/0·5 h)	Change during sampling period (%)	Statistical significance (*P*)
[^{14}C]glucose	Portal	Pregnant	2·62	0·11	0·08	9·8	NS
		Lactating	3·46	0·21	0·25	23·9	NS
	Hepatic	Pregnant	3·04	0·12	−0·05	−4·9	NS
		Lactating	3·95	0·20	0·18	14·4	NS
[^{14}C]lactate	Portal	Pregnant	2·76	0·11	−0·07	−7·0	NS
		Lactating	3·73	0·15	−0·08	−6·0	NS
	Hepatic	Pregnant	3·01	0·13	−0·13	−11·8	NS
		Lactating	4·33	0·28	0·06	4·6	NS

NS, not significant. Statistical significance taken to be achieved at $P < 0·05$.

RESULTS

Experimental conditions

Values for blood flow rate showed no consistent change over the last 1·5 h of isotope infusion and were similar whether labelled glucose or labelled lactate was infused (Table 1). Since blood concentrations and specific activities of metabolites also remained relatively constant over this period (Baird *et al.* 1983), it was considered that equilibrium pertained approximately and that steady-state equations could therefore be applied.

Blood flows through both the portal-drained viscera and liver increased by some 30–40% from pregnancy to lactation (Table 1). The small standard errors for the mean values (usually about 5% of the mean), showed that conditions were comparable between experiments and that the differences between the blood flow values obtained during the two physiological states were real.

Mean arterial values obtained for glucose and lactate concentrations and specific activities are summarized in Table 2, as are the differences between various vessels. The errors associated with determining veno-arterial differences are high for single sampling times. However, by taking means of multiple samples, these errors were reduced and, besides this, the between-experiment repeatability of veno-arterial differences was increased. On the whole, similar concentrations as well as blood flow rates were obtained during the [^{14}C]glucose and [^{14}C]lactate infusions, and many of the veno-arterial differences in concentration and radioactivity were statistically different from zero.

Metabolism by splanchnic viscera and peripheral tissues

Rates of net exchange of glucose and lactate across the various tissues are recorded in Table 3. Also included in this table are the rates of net exchange of alanine and pyruvate. These two compounds can be expected to have a close metabolic relationship to lactate and have, like lactate, been implicated in the recycling of glucose-C (e.g. Foster *et al.* 1980). It is evident that net output of glucose from the liver was greater during lactation than during pregnancy, as was net uptake by the hind-quarters. During both pregnancy and lactation there was also a small net output of glucose from the gut. During lactation, output of lactate from the gut was higher than during pregnancy, presumably because the lactating animals were

Table 2. *Mean blood flow and concentrations and radioactivities of glucose and lactate when [^{14}C]glucose or [^{14}C]lactate were infused*

(Mean values with their standard errors. All radioactivity values are adjusted for an infusion rate of 30 μCi/h. Positive concentration differences indicate net production and positive radioactivity differences indicate utilization)

			Concentration (μM)								Radioactivity (nCi/l)							
			A		P−A		H−A		V−A		A		A−P		A−H		A−V	
Metabolite measured	No. of infusions	Status	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
[^{14}C]glucose infused																		
Glucose	5	Pregnant	2579	179	46	25	235**	28	−138*	20	1495	128	25·3	16·0	24·1	12·8	101***	19
	3	Lactating	3825	250	41	15	268*	59	−282*	69	1488	162	23·2	5·9	26·7	7·7	129*	18
Lactate	5	Pregnant	478	33	52**	11	−105***	8	58**	7	108	7	2·0	4·2	34·2**	4·1	−7·2	3·2
	3	Lactating	632	55	76*	17	−27	20	15	37	74	9	−5·4	3·5	0·9	6·2	−15·0	2·9
[^{14}C]lactate infused																		
Glucose	5	Pregnant	2860	238	18	9	197***	31	−126**	16	484	24	−2·2	7·1	−28·0*	8·1	20·2*	5·8
	3	Lactating	3788	59	−20	13	179**	8	−344	89	248	45	2·7**	0·1	−5·7***	0·1	19·6**	1·3
Lactate	5	Pregnant	572	59	53	15	−125*	27	53*	15	462	36	−3·2	15·3	134·2**	15·8	13·9	15·0
	3	Lactating	662	59	73**	3	−13	13	26	33	433	48	36·5*	6·8	92·2*	10·5	68·5	27·3

A, artery; P, portal; H, hepatic; V, lower vena cava.

*$P < 0·05$, **$P < 0·01$, ***$P < 0·001$, for significance of difference from zero, by Student's t test.

Table 3. *Rates of net exchange of metabolites (mmol/h) across the portal-drained viscera, liver and hind-quarters (HQ)*

(Mean values with their standard errors obtained during the number of separate infusions indicated. Positive exchange values indicate output, and negative indicate uptake. The values include those obtained in a parallel study using the same animals (J. G. van der Walt, G. D. Baird and E. N. Bergman, unpublished results))

Metabolite	Ewe status	No. of infusions	Portal viscera		Liver		HQ		Peripheral tissues‡	Hepatic extraction (%)		Lactate output from HQ relative to glucose uptake (%)	
			Mean	SE	Mean	SE	Mean	SE	Mean	Mean	SE	Mean	SE
Glucose	Pregnant	11	6·1	2·3	32·8	2·7	−11·1	1·2	−38·8	—	—	—	—
	Lactating	7	4·7	3·0	56·0*	5·8	−28·3†	3·9	−60·7	—	—	—	—
Lactate	Pregnant	11	9·1	1·4	−28·1	2·8	5·5	0·7	19·0	29	3	56	9
	Lactating	7	16·1	1·0	−22·8	3·0	2·9	1·8	6·7	14	2	15*	7
Pyruvate	Pregnant	8	0·2	0·2	−1·4	0·3	0·6	0·1	1·2	34	7	—	—
	Lactating	6	−0·1	0·4	0·5	1·0	0·6	0·3	−0·4	−8*	14	—	—
Alanine	Pregnant	5	3·2	0·7	−3·2	0·6	0·6	0·2	0·0	24	5	—	—
	Lactating	4	4·9	0·8	−3·9	0·3	−0·4*	0·2	−1·0	10*	1	—	—

†$P < 0·10$ and *$P < 0·05$ as compared with the corresponding pregnant group.

‡ Peripheral values include those of the HQ and, since near steady-state conditions existed, were calculated by equating total net splanchnic (portal visceral + hepatic) production to total net peripheral utilization (Wolff & Bergman, 1972).

Table 4. *Glucose and lactate turnover and metabolism by individual tissues*

(Mean values with their standard errors, no. of experiments given in parentheses)

Ewe status	Metabolite (no. of experiments)	Whole-body turnover (mmol/h)				Flux (mmol/h)											
						Portal viscera				Liver				Hind-quarters			
		Apparent		Corrected‡		Utilized		Produced		Utilized		Produced		Utilized		Produced	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Pregnant	Glucose (5)	54·1	6·6	54·1	6·6	8·8	5·1	13·1	4·7	1·1	3·7	35·8	4·9	18·4	4·0	6·0	2·5
	Lactate (5)	37·6	3·9	40·1	5·0	−0·2	3·5	8·5	3·8	33·3	4·9	2·2	4·6	1·8	1·6	6·6	1·6
Lactating	Glucose (3)	79·9	13·5	79·6	13·2	15·8	8·3	25·6	12·5	−0·6	11·0	55·7†	4·7	32·3	10·0	6·9	4·5
	Lactate (3)	45·9	0·8	51·0	0·5	14·4*	2·0	30·1**	2·0	29·0	0·1	10·7	3·1	12·3†	2·9	12·8*	0·8

† $P < 0{\cdot}10$, * $P < 0{\cdot}05$ and ** $P < 0{\cdot}01$ as compared with corresponding pregnant values.

‡ Corrected by adding the amount of metabolite absorbed into the portal blood that was immediately removed by the liver.

consuming more feed. The percentage hepatic extraction of lactate was less during lactation, as was lactate output from the hind-quarters expressed as a percentage of glucose uptake. Decrease in hepatic extraction during lactation was also seen for pyruvate and alanine. While there was a net output of alanine across the hind-quarters during pregnancy, there was a net uptake during lactation. Clearly, the net exchanges of alanine, and even more so of pyruvate, are small as compared with those of lactate.

Values for unidirectional utilization and production rates of glucose and lactate by the various tissues, together with whole-body apparent and corrected turnover rates, are listed in Table 4. That practically none of the newly absorbed glucose in the portal circulation was removed by the liver, presumably due to the absence of glucokinase (*EC* 2.7.1.2) in this organ (Ballard *et al.* 1969; Bergman *et al.* 1974), is reflected in the close correspondence of the apparent and corrected ^{14}C turnover values (Table 4). However, the apparent turnover of lactate underestimated the corrected turnover by about 6% during pregnancy and about 10% in lactating animals; this was due to percentage hepatic extraction values for lactate of between 14 and 29 (Table 3).

As would be expected, both whole-body glucose turnover and liver production of glucose were higher during lactation than during pregnancy. Utilization of glucose by the hind-quarters also appeared higher during lactation than during pregnancy. During lactation the portal-drained viscera also seemed an important site of glucose utilization.

Lactate turnover seemed to be somewhat higher during lactation than during pregnancy. In both physiological states the liver was quantitatively the most important site of utilization of lactate, although during lactation the portal-drained viscera and hind-quarters also appeared to utilize significant quantities. During pregnancy the main sites of lactate production were the viscera and the hind-quarters, while during lactation the viscera seemed more important.

When the previously mentioned results are expressed as percentages of the corrected turnover rate in each case (Table 5), differences between the tissue metabolic patterns of glucose and lactate become more apparent. The glucose metabolism patterns seemed similar during both pregnancy and lactation with 66–70% produced by liver and 24–32% by the portal viscera. Interestingly, the hind-quarters seemed to produce small amounts of glucose (9–11%) in both cases, although systematic errors of summation could possibly have accounted for this. The lactate patterns, however, were different. Comparison of the lactating and pregnant animals indicates that during lactation lactate production from the portal-drained viscera was increased (from 21 to approximately 60%), as it was from the liver (from 5 to 21%), at the expense of production from peripheral sources (which declined from 73 to 20%). At the same time, utilization of lactate by the portal-drained viscera definitely seemed to increase (from zero to approximately 30%), as did utilization by the hind-quarters (from 4 to 24%). These latter increases apparently occurred at the expense of liver utilization (which declined from 83 to 57%).

Recycling and interconversions of glucose and lactate

The values for glucose and lactate metabolism summarized previously could be minimal if significant recycling of ^{14}C had occurred. Transfer of ^{14}C between glucose and lactate was therefore determined by analysing the specific activity of each metabolite during both the [^{14}C]glucose and [^{14}C]lactate infusion series. The extent of recycling and interconversions between glucose and lactate were then calculated as described previously. Solutions to the simultaneous equations are illustrated in Fig. 1, the rates being expressed as mg atoms C/h. The results are summarized further in Table 6 to show the percentage contribution of the various tissues to the whole-body turnover rate.

Generally, interconversions between the two metabolites were significant and were

Table 5. *Tissue fluxes of glucose and lactate expressed as percentage of corrected turnover rates*
(Mean values with their standard errors)

				Flux of metabolite (% of corrected turnover)													
				Portal viscera				Liver				Hind-quarters				Peripheral tissues†			
				Utilized		Produced		Utilized		Produced		Utilized		Produced		Utilized		Produced	
Metabolite	Ewe status	No. of expts	Corrected turnover* (mmol/h)	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Glucose	Pregnant	5	54·1	16	9	24	9	2	7	66	9	34	7	11	5	82	6	10	10
	Lactating	3	79·6	20	10	32	16	−1	14	70	6	41	13	9	6	81	20	−2	3
Lactate	Pregnant	5	40·1	−1	9	21	10	83	12	5	11	4	4	16	4	17	10	73	9
	Lactating	3	51·0	28	4	59	5	57	1	21	6	24	5	25	1	15	5	20	1

* Corrected by adding the amount of metabolite absorbed into the portal blood that was immediately removed by the liver.
† Peripheral values include those of the hind-quarters and were obtained by subtracting the total splanchnic (portal visceral+hepatic) utilization or production percentages from 100.

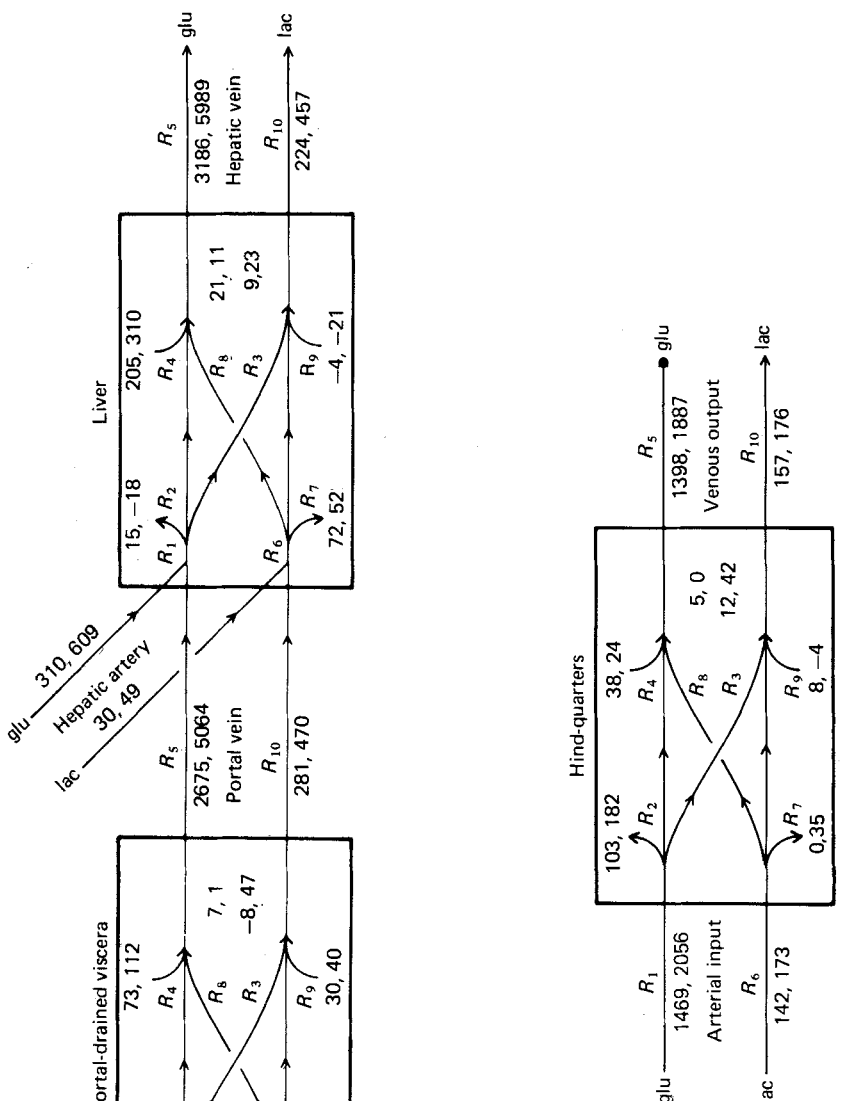

Fig. 1. Schematic diagram of unidirectional utilization and production, and interconversions, of glucose (glu) and lactate (lac) in different tissues. Values for rates (R_1–R_{10}; mg atoms carbon/h) are means for pregnant and lactating sheep respectively.

Table 6. *Summary of glucose and lactate metabolism and interconversions*

Ewe status	Tissue	% of corrected glucose turnover				% of corrected lactate turnover			
		Glucose util. (R_2+R_3)	Glucose prod. (R_4+R_8)	To lactate (R_3)	From lactate (R_8)	Lactate util. (R_7+R_8)	Lactate prod. (R_3+R_9)	To glucose (R_8)	From glucose (R_3)
Pregnant	PDV	17	25	−3	2	−3	17	5	−6
	Liver	8	70	3	7	73	4	17	7
	HQ	36	14	4	2	4	13	4	9
	Periphery†	85	15	31	3	28	76	8	78
	Total body	110	110	31	12	98	97	30	79
Lactating	PDV	20	23	10	0	26	57	1	31
	Liver	1	67	5	2	42	1	7	15
	HQ	41	5	9	0	23	25	0	28
	Periphery†	83	13	4	4	27	36	8	11
	Total body	104	103	19	6	95	94	16	57

R_2-R_4 and R_7-R_9, for details see Fig. 1.
PDV, portal-drained viscera; HQ, hind-quarters; util., utilized; prod., produced.
† Includes hind-quarters.

influenced by the physiological state of the ewe. During pregnancy, 31% of the corrected glucose turnover went into lactate production mainly in peripheral tissues while 12% was in turn derived from lactate, chiefly in liver. Lactation halved these interconversions. While the total glucose utilized was equal to the amount produced, these values exceeded the corrected turnover rates by 10 and 4% during pregnancy and lactation respectively. This, therefore, confirms that some ^{14}C recycling was taking place and is an indication of the magnitude of the resultant underestimation of total glucose turnover.

In parallel with the results for glucose turnover, the percentages of lactate turnover converted to or derived from glucose were greater during pregnancy (30 and 79% respectively) than during lactation (16 and 57% respectively). Furthermore, while there seemed to be one major site for each interconversion in the pregnant animals, i.e. the liver for conversion to glucose and the peripheral tissues for derivation from glucose, several sites seemed to be involved in the interconversions in the lactating animals. The interconversions between glucose and lactate, however, did not greatly affect the estimates of corrected lactate turnover, since approximately 98 and 95% of the total lactate turnover was accounted for during pregnancy and lactation respectively.

Values for glucose turnover rate that were derived from the simultaneous infusions of [U-^{14}C]- and [6-^{3}H]glucose are summarized by Baird *et al.* (1983). Included in the latter paper are values for percentage glucose recycling that were calculated from the differences in turnover rate obtained with the two isotopes. The recycling rates for glucose during pregnancy (6%) and lactation (2%) appear to be comparable to, or only slightly less than, values obtained from the model values of Table 6 (10 and 4% respectively). It can thus be concluded that recycling of ^{14}C between glucose and lactate definitely does occur in the ruminant, but underestimation of glucose turnover is only of the order of 4–10%.

DISCUSSION

The present paper presents quantitative values for unidirectional rates of metabolism of glucose and lactate and interconversions of these compounds in several tissues. The mathematical models and techniques used were similar to those previously developed in this laboratory to investigate the metabolism of amino acids (Wolff & Bergman, 1972). In line with this previous study, apparent whole-body turnover rates were corrected for the immediate hepatic utilization of glucose and lactate absorbed by the gut. Since ovine liver does not utilize glucose to any significant extent (Ballard *et al.* 1969; Bergman *et al.* 1974), apparent whole-body turnover rates for this compound closely approximated corrected turnover. However, the considerable uptake of lactate by the liver definitely leads to an underestimation of lactate turnover. In our experiments, this underestimation amounted to 6–10%.

Earlier work by Reilly & Chandrasena (1978) in non-pregnant, non-lactating ewes showed a positive correlation between plasma concentrations of both glucose and lactate and their respective turnover rates. They further observed that the amount of glucose formed from lactate also correlated with lactate turnover and the conclusion was logically drawn that arterial concentration of lactate plays a significant role in regulating the rate of production of glucose. Our results do not support these findings as far as comparisons between the two physiological groups are concerned, since 12% (i.e. 6·5 mmol/h) and 6% (i.e. 4·8 mmol/h) of glucose turnover was derived from lactate during pregnancy and lactation respectively (Table 6), when the lactate concentrations were similar, i.e. 0·50 and 0·58 mM respectively (Baird *et al.* 1983).

Glucose metabolism by the splanchnic viscera was similar in most respects to results previously obtained in this laboratory (Bergman *et al.* 1974), with the exception of the

amount of glucose produced by the portal-drained viscera. Earlier results obtained on pregnant ewes given only lucerne hay showed a net utilization of glucose by the portal-drained viscera, mainly due to a lack of any measurable unidirectional production. In the present study, however, a unidirectional output was detected, amounting to 24–32% (Table 5) of the glucose turnover rate. The small but significant contribution of glucose from the portal-drained viscera thus seems to stem from the diet used. In the present study, the grain concentrate present in the diet could be expected to provide at least some glucose which by-passes fermentation in the rumen and utilization by gut tissues. In all cases, nevertheless, the liver remained the major source of glucose and contributed at least two-thirds of the total glucose supply.

While the hind-quarters showed a large uptake of glucose, the results did also indicate a small but nearly consistent unidirectional production of glucose from this site (Table 4). This observation simply may have arisen as a result of systematic errors of summation in the various calculations. However, some glucose-6-phosphatase (*EC* 3.1.3.9) activity has recently been demonstrated in many peripheral tissues, including muscle (Rosen, 1974; Surholt & Newsholme, 1981). If this enzyme is indeed physiologically active in peripheral tissues, some escape of unlabelled glucose could occur and be reflected in the present results as production.

Although all the ewes were fed to recommended levels (Ministry of Agriculture, Fisheries and Food, 1975), they appeared to be in a higher state of glucose sufficiency during lactation than during pregnancy (Baird *et al.* 1983). Thus, despite the glucose demand of milk production the ewes exhibited higher blood glucose concentrations, and higher rates of glucose utilization by the hind-quarters, during lactation than during pregnancy (Baird *et al.* 1983 and Table 4). Unidirectional production of lactate by the hind-quarters (Table 4) also increased in proportion to the increase in glucose uptake, pointing in turn to an increase in the relative contribution of glucose to the energy metabolism of muscle tissue. However, the loss of the pregnant uterus as an important source of lactate (Baird *et al.* 1983) leaves the portal-drained viscera as the major single source of lactate during lactation (Table 6).

The glucose–lactate interconversion results showed that despite extensive interconversions of C atoms, the whole-body turnovers, corrected for hepatic extraction of newly absorbed metabolite, were underestimated by only 4–10% in the case of glucose and overestimated by only 2–5% in the case of lactate (Table 6). Furthermore, the apparent decrease in interconversions during lactation was confirmed by the [U-^{14}C]glucose plus [6-^{3}H]glucose values, which showed a reduction in glucose recycling from 6 to 2%. As indicated previously, the apparent amount of glucose formed from lactate decreased by approximately 25% in absolute terms during lactation despite an increase of approximately 50% in glucose turnover. The results suggest that this was due to the decreased uptake of lactate by the liver during lactation. Since the ewes received more energy in their diet during lactation, the increased gluconeogenesis must have been fuelled mainly by the resultant rise in rumen propionate production, so that lactate was spared (van der Walt, 1978).

Lactate thus does not appear to be quantitatively an important precursor of glucose. Only 7% of the glucose turnover was calculated to be derived from lactate in the liver of pregnant sheep and this fraction became even smaller during lactation (2%) (Table 6). Furthermore, only 17 and 7% respectively of the lactate turnover was calculated to be converted to glucose in the liver during pregnancy and lactation. Even if these are minimal values, as discussed earlier, most of the lactate in the liver must surely be left available for oxidation or for various alternative anabolic pathways (Prior & Jacobson, 1979).

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REFERENCES

Baird, G. D., Lomax, M. A., Symonds, H. W. & Shaw, S. R. (1980). *Biochemical Journal* **186**, 47–57.
Baird, G. D., van der Walt, J. G. & Bergman, E. N. (1983). *British Journal of Nutrition* **50**, 249–265.
Ballard, F. J., Hanson, R. W. & Kronfeld, D. S. (1969). *Federation Proceedings* **28**, 218–231.
Bergman, E. N., Brockman, R. P. & Kaufman, C. F. (1974). *Federation Proceedings* **33**, 1849–1854.
Bergman, E. N., Roe, W. E. & Kon, K. (1966). *American Journal of Physiology* **211**, 793–799.
Bergman, E. N., Starr, D. J. & Reulein, S. S. (1968). *American Journal of Physiology* **215**, 874–880.
Brockman, R. P. & Bergman, E. N. (1975). *American Journal of Physiology* **228**, 1627–1633.
Brockman, R. P., Bergman, E. N., Pollak, W. L. & Brondum, J. (1975). *Canadian Journal of Physiology and Pharmacology* **53**, 1186–1189.
Corse, D. A. & Elliot, J. M. (1970). *Journal of Dairy Science* **53**, 740–746.
Foster, D. M., Hetenyi, G. Jr & Berman, M. (1980). *American Journal of Physiology* **239**, E30–E38.
Heitmann, R. N. & Bergman, E. N. (1981). *American Journal of Physiology* **241**, E465–E472.
Judson, G. J., Anderson, E., Luick, J. R. & Leng, R. A. (1968). *British Journal of Nutrition* **22**, 69–75.
Judson, G. J. & Leng, R. A. (1972). *Australian Journal of Biological Science* **25**, 1313–1332.
Katz, M. L. & Bergman, E. N. (1969*a*). *American Journal of Veterinary Research* **30**, 655–661.
Katz, M. L. & Bergman, E. N. (1969*b*). *American Journal of Physiology* **216**, 946–952.
Krebs, H. A., Hems, R., Weidemann, M. J. & Speake, R. N. (1966). *Biochemical Journal* **101**, 242–249.
Lindsay, D. B. (1970). In *Physiology of Digestion and Metabolism in the Ruminant*, pp. 438–451 [A. T. Phillipson, editor]. Newcastle upon Tyne: Oriel.
Ministry of Agriculture, Fisheries and Food (1975). *Technical Bulletin* no. 33. London: H.M. Stationery Office.
Prior, R. L. & Jacobson, J. J. (1979). *Journal of Animal Science* **49**, 1410–1416.
Reilly, P. E. B. & Chandrasena, L. G. (1978). *American Journal of Physiology* **235**, E487–E492.
Rosen, S. I. (1974). *Acta Histochemica* **50**, 1–18.
Surholt, B. & Newsholme, E. A. (1981). *Biochemical Journal* **198**, 621–629.
van der Walt, J. G. (1978). *Onderstepoort Journal of Veterinary Research* **45**, 125–132.
Wilson, S., MacRae, J. C. & Buttery, P. J. (1981). *Research in Veterinary Science* **30**, 205–212.
Wolff, J. E. & Bergman, E. N. (1972). *American Journal of Physiology* **223**, 447–454.

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