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Splanchnic Uptake and Release of Energy Substrates in the Fasting Baboon Infant

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ABSTRACT. Estimates of splanchnic energy substrate exchange in the primate infant have been obtained using a baboon model. The splanchnic bed of the fasting baboon newborn released glucose at an estimated rate of 14.5 ± 5.0 μmol/min·kg body weight. Splanchnic glucose release in the fasting 5–7-wk old baboon infant proceeded similarly at an estimated rate of 15.5 ± 4.5 μmol/min·kg body weight. The principal precursors taken up by the splanchnic bed were lactate, glycerol, and alanine. Uptake of alanine correlated in a linear fashion with glucose release. Lactate was the most important precursor in both age groups. Glucose recycling through lactate is an active mechanism in the primate fetus as well as in the young of other species. (*Pediatr Res* 18:1316–1320, 1984)

Abbreviations

HV, estimated hepatic vein concentration
A, arterial concentration
V_1, inferior vena cava concentration below the hepatic vein
V_2, inferior vena cava above the hepatic vein
F_{LC}, inferior vena cava flow below the hepatic vein
F_{SP}, splanchnic flow

Quantitative data concerning splanchnic energy metabolism are readily available in adult man (5, 9, 23, 25, 31). In contrast, information regarding splanchnic substrate exchange in the neonate and infant is derived entirely from studies in subprimate species (3, 11, 24, 29, 30), isolated fetal organ studies (1, 2, 10), or inferential data derived from infusion studies, tolerance tests (6, 14), and stable isotope methodology (15). Previous investigations using the newly born baboon as a model for the study of neonatal energy metabolism suggest that this animal resembles the small-for-gestational-age human infant in terms of response to fasting and diminished body fat (19, 20). Fasting plasma arterial levels of energy substrates in the newborn of this species are similar to those found in the stressed small-for-gestational-age human neonate. Further, cerebral uptake of energy substrates is similar to that observed in human infants (19). Therefore, in the present study, we have utilized the infant baboon in order to derive estimations of comparative splanchnic energy substrate exchange in a clinically relevant model.

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MATERIALS AND METHODS

Experimental animals and procedure. Baboon neonates obtained from the University of Illinois Primate Colony (Chicago IL) were the products of timed matings. Six were delivered by cesarean section at term after a 175–180-day gestation and studied at 6 to 8 h of life. Two of these animals were then maintained in infant incubators and fed commercial infant formula (Similac, Ross Laboratories) until studied again at 5 to 7 wk of life. Three other baboon neonates, products of spontaneous deliveries, were studied for the first time at 5 to 7 wk of life.

Under local xylocaine anesthesia, catheters (PV3, Biolabs) were placed in the aorta, the left ventricular outflow tract, and in the inferior vena cava above and below the level of the hepatic vein (Fig. 1). Catheters were kept patent with heparinized saline (1 unit heparin/ml). Animals were maintained under a radiant warmer during procedures and restrained, but not sedated. The stability of the animals was assessed by the stability of arterial pH, oxygen content, lactate, hematocrit, cardiac output, and organ blood flows. Newborns were fasted from birth; animals studied at 5 to 7 wk of life were similarly fasted for 6 to 8 hr.

Studies were carried out 2 to 4 hr following catheter placement. Six to eight sets of three 1-ml samples obtained from the aorta, the inferior vena cava above and below the hepatic vein were

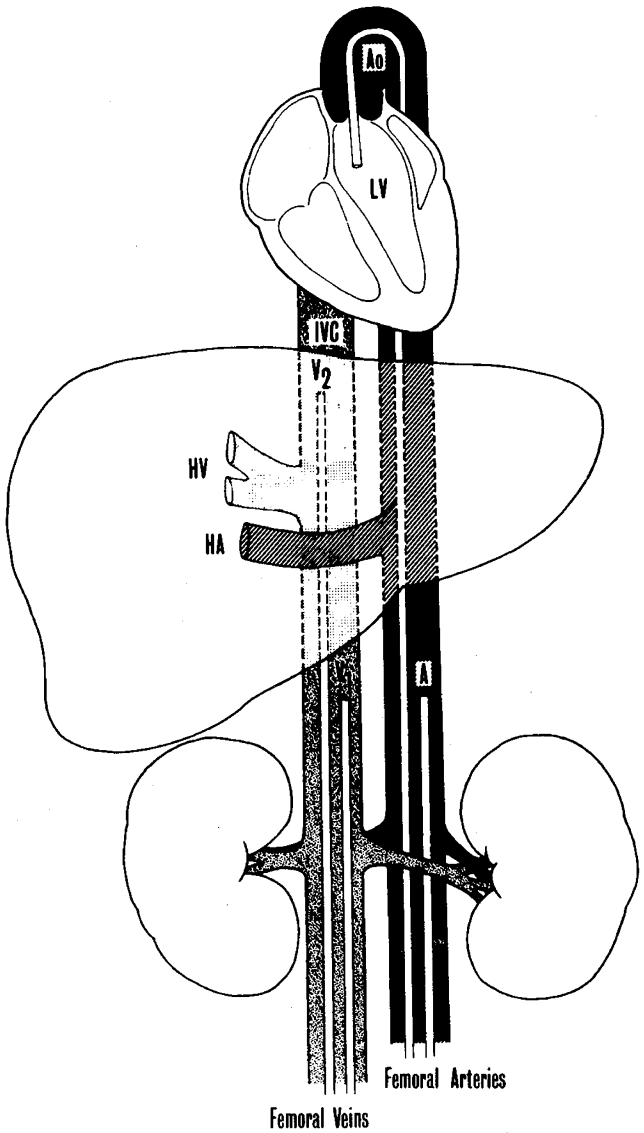

Fig. 1. Placement of catheters in the baboon infant in order to determine levels of substrates in the abdominal aorta (*A*), and in the inferior vena cava (*IVC*) above (V_2) and below (V_1) the level of the hepatic vein (*HV*). The hepatic artery (*HA*), thoracic aorta (*Ao*), and left ventricle (*LV*) are indicated. Catheters were placed through the femoral vessels.

Table 1. *Protocol for time and volume of blood sampling and cardiac output determinations*

Time (min)	Procedure	Amount of blood from each site (ml)	Total blood withdrawn (ml)
0	Substrate sample 1	1	3
5	Blood gas sample 1	1	3
15	Injection of microspheres	2 (aortic only)	2
30	Substrate sample 2	1	3
50	Substrate sample 3	1	3
60	Blood gas sample 2	1	3
70	Substrate sample 4	1	3
80	Injection of microspheres	2 (aortic only)	2
90	Substrate sample 5	1	3
100	Blood gas sample 3	1	3

used for substrate and blood gas determinations according to the protocol in Table 1. Blood was replaced volume for volume with heparinized placental or maternal blood in all infants following each sampling interval.

Analytic methods. Plasma samples were analyzed for glucose using a glucose oxidase oxygen electrode technique (Beckman) and for glycerol (18), lactate (22), pyruvate, alanine (16), and D-β-hydroxybutyrate (28) using enzymatic fluorometric methods. Samples for pyruvate were analyzed immediately. Others were frozen at −70° C until analysis. All samples except those for glucose were assayed after preparation of a 1:10 dilution of a protein-free filtrate using Centriflo membrane cones (CF-50, Amicon). All analyses of each sample were performed in triplicate, but not all substrate analyses were performed on each specimen. Each replicate set of three values (A, V_1, V_2) was analyzed in the same assay run. Replicate assays were rejected and repeated if determinations varied more than 5% from the mean value. Mean values for these determinations are reported. Blood gas determinations were performed using Radiometer electrodes and meter PMH 71. The pH, and P_{O_2} were measured directly. Oxygen content was calculated from a previously developed nomogram (27). Cardiac output and organ blood flows were computed using a radioactive microsphere technique and up to four determinations were made using different isotopic labels (26). For every study in each animal, the means of two flow measurements were used to calculate hepatic vein concentration of substrates and oxygen, and, by extension, substrate flux as well as oxygen uptake. Plasma flows were determined using a correction for hematocrit. Because hepatic vein catheterization has not proved technically feasible in this preparation, the following formula utilizing the Fick principle was employed to derive estimates of HV, based upon determinations of F_{LC}, F_{SP}, and substrate concentrations V_2 and V_1. This formula cannot be validated in the neonatal baboon, but values for glucose production derived by this technique agree well with previous data for glucose turnover in the neonate and hepatic glucose production in adult humans (4, 5, 7, 9, 15).

$$[HV] = \frac{[V_2]\,(F_{LC} + F_{SP}) - [V_1]\,(F_{LC})}{F_{SP}}$$

Splanchnic flow was defined as the sum of hepatic, splenic, pancreatic, and gastrointestinal flows. Calculations of hepatic vein concentrations for each animal are the means of separate computations for each set of simultaneous samples (A, V_1 V_2) utilizing the mean of two blood flow determinations. Arterial and venous plasma substrate levels at different ages were compared using the two-tailed Student's *t* test. Significance of arteriohepatic venous differences for substrates was assessed by one-way analysis of variance. Arteriohepatic venous differences in the neonates and older infants were similarly evaluated by assessing intergroup variance. Comparison of lactate and alanine uptake and glucose production were made using linear regression analysis.

Enzymes for substrate analysis were obtained from Boehringer-Mannheim, New York (glycerokinase, glycerophosphate dehydrogenase) and Sigma, St. Louis, MO (lactic dehydrogenase, D-β-hydroxybutyrate dehydrogenase, glutamic-pyruvic transaminase). Reagents used to construct standard curves were purchased from Sigma (lactic acid, DL-β-hydroxybutyrate, ketoglutarate, alanine, pyruvate), and Sargent-Welch, Chicago, IL (glycerol). NADH and NAD were purchased from Sigma. Fluorometric analyses were performed on an Aminco-Bowman SPF-15 spectrophotofluorometer. Radioactive microspheres were obtained from 3M, Minneapolis, MN.

RESULTS

The mean body weight, hepatic weight, cardiac output, blood and plasma splanchnic flows, and hematocrit of the baboon infants are shown in Table 2.

Substrate levels, pH, oxygen content, and organ blood flows remained stable in each animal over the sampling period. The mean arterial lactate, oxygen content, and hematocrit at the beginning and end of the study were not significantly different. In the neonate, pH at the beginning of the study was 7.31 ± 0.01

Table 2. *Weights and hemodynamic characteristics of baboon infants (mean ± SE)*

Age	Body weight (g)	Hepatic weight (g)	Cardiac output (ml/min)	Adjusted cardiac output (ml/min·kg)	Blood splanchnic flow (ml/min)	Hematocrit (%)	Plasma splanchnic flow (ml/min)
Newborn ($n = 6$)	800 ± 57	(23.9)*	93.3 ± 8.3	116.4 ± 5.9	35.2 ± 5.2	45.8 ± 1.5	18.7 ± 3.1
5–7 wk ($n = 5$)	1021 ± 57	29.5 ± 4.5	168.2 ± 12.9	162.5 ± 12.6	50.9 ± 6.4	34.8 ± 1.4	33.2 ± 4.2

* Only one hepatic weight was obtained in this group. All other animals were not immediately sacrificed because of plans for repeated studies at 5–7 wk. Those so studied had catheters re-inserted as described.

Table 3. *Levels of plasma substrates, and oxygen (mM ± SE) in the aorta, and the inferior vena cava above and below the hepatic vein: calculated hepatic vein values and substrate flux*

	A	V_1	V_2	Calculated HV	HV-A	Substate and oxygen exchange (μmol/min·kg body weight)
Newborn						
Glucose	3.11 ± 0.21	2.74 ± 0.16	3.40 ± 0.28	3.75 ± 0.39	0.64 ± 0.24	11.4 ± 4.2
Lactate	2.46 ± 0.48	4.28 ± 0.85	2.23 ± 0.27	1.17 ± 0.56	−1.21 ± 0.54	−20.3 ± 10.5
Alanine	0.329 ± 0.023	0.387 ± 0.018	0.300 ± 0.010	0.252 ± 0.023	−0.077 ± 0.034	−1.35 ± 0.72
Pyruvate	0.032 ± 0.007	0.062 ± 0.014	0.050 ± 0.009	0.032 ± 0.013	−0.0027 ± 0.0086	−0.054 ± 0.110
β-OH-butyrate	0.115 ± 0.006	0.142 ± 0.023	0.125 ± 0.010	0.191 ± 0.007	−0.021 ± 0.006	−0.329 ± 0.088
Glycerol	0.157 ± 0.019	0.190 ± 0.032	0.116 ± 0.014	0.078 ± 0.024	0.085 ± 0.039	1.38 ± 0.54
Oxygen	7.02 ± 0.20	4.09 ± 0.50	5.08 ± 0.21	5.55 ± 0.32	−1.48 ± 0.28	−26.9 ± 5.1
5–7 wk						
Glucose	2.24 ± 0.20	2.24 ± 0.22	2.51 ± 0.16	2.71 ± 0.16	0.46 ± 0.10	16.1 ± 4.9
Lactate	1.00 ± 0.43	1.17 ± 0.55	0.874 ± 0.39	0.639 ± 0.301	−0.364 ± 0.212	−12.5 ± 7.9
Alanine	0.124 ± 0.019	0.138 ± 0.008	0.096 ± 0.014	0.065 ± 0.019	−0.063 ± 0.016	−2.04 ± 0.62
Pyruvate	0.043 ± 0.011	0.043 ± 0.011	0.029 ± 0.003	0.017 ± 0.005	−0.024 ± 0.016	−0.858 ± 0.571
β-OH-butyrate	6.06 ± 0.98	5.77 ± 75	6.11 ± 0.38	6.301 ± 0.00	0.10 ± 0.27	0.71 ± 8.9
Glycerol						
Oxygen	5.07 ± 0.41	3.95 ± 0.46	3.62 ± 0.50	3.58 ± 0.64	−1.50 ± 0.69	−68.6 ± 28.0

Table 4. *Estimated gluconeogenic equivalents taken up by the splanchnic bed and glucose production (μmol/min ± SE)*

	Lactate	Alanine	Pyruvate	Glycerol	Total	Glucose
Newborn	10.2 ± 5.3	0.68 ± 0.36	0.027 ± 0.055	0.69 ± 0.27	11.6 ± 5.9	11.4 ± 4.2
5–7 wk	6.2 ± 4.0	1.02 ± 0.31	0.429 ± 0.286		7.65 ± 4.60	16.1 ± 4.9

and at the end of the study was 7.32 ± 0.02. In the older infant, pH was 7.37 ± 0.04 at the beginning of the study and 7.36 ± 0.03 at the end of the study; there were no significant differences over the course of the study. The mean arterial plasma glucose in the fasting newborns was 3.11 mM or 56 mg/dl, while in the 5- to 7-wk-old infants it was 2.24 mM or 40.3 mg/dl. This was significantly lower ($p < 0.025$).

The mean measured levels of glucose and other plasma substrates in the aorta and in the inferior vena cava above and below the hepatic vein, as well as estimated hepatic vein substrate levels, arteriohepatic venous differences, and mean computed substrate flux based on plasma splanchnic flow are detailed in Table 3. Arterial plasma alanine ($p < 0.001$) and lactate ($p < 0.025$) levels were significantly higher in the newborns compared to the older infants, and β-hydroxybutyrate was significantly higher ($p < 0.001$) in the older infants. Arterial oxygen content was higher ($p < 0.005$) in the newborn than older infants because of the higher hematocrits in the younger animals.

Arteriohepatic venous substrate differences were analyzed for significance using one-way analysis of variance. Release of glucose and uptake of lactate, alanine, and pyruvate were significant in both newborn and older animals ($p < 0.005$). β-Hydroxybutyrate was produced by the splanchnic bed of the neonate and glycerol was taken up ($p < 0.01$). Plasma β-hydroxybutyrate in the older animals was quite high, but no pattern of net uptake or release could be discerned. Glycerol was not measured in the older animals. Estimated glucose release was 14.5 ± 5.0 μmol/min·kg (95% confidence limits, 1.6 to 27.4 μmol/min·kg) in the newborn baboon and 15.5 ± 4.5 μmol/min·kg body weight (95% confidence limits, 3.1 to 27.9 μmol/min·kg) in the 5- to 7-wk-old infants.

Arterial lactate levels correlated in a linear fashion with splanchnic lactate uptake in the animals in both age groups ($p < 0.05$) (Fig. 2). Further, arterial lactate levels were linearly related to glucose release in the neonates ($p < 0.05$) (Fig. 3), although not in the 6-wk animals (5). Alanine uptake correlated with glucose release in a linear fashion in the group as a whole ($p < 0.01$) (Fig. 4). Oxygen uptake did not correlate with glucose production.

DISCUSSION

Fasting arterial plasma levels in these neonates were compatible with similar data obtained in human neonates. Plasma alanine levels in older infants were similar to values found in fasted older children (24), whereas neonatal values approximated those previously found in human neonates (13). Arterial lactate levels were high, but in the range seen in the physically stressed human neonate.

Because it is impossible to successfully catheterize the hepatic or umbilical vein and obtain unpooled blood in these tiny animals, all measures of hepatic vein substrate levels must be

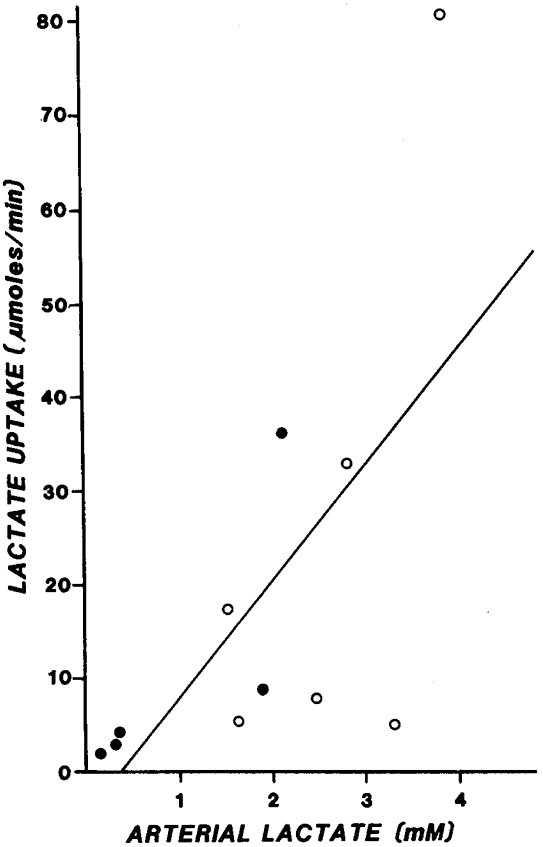

Fig. 2. Relationship of arterial lactate levels to splanchnic lactate uptake. O, neonates; ●, older infants ($r = 0.65$, $p < 0.05$ for both groups; $r = 0.64$, neonates, and $r = 0.76$, older infants; NS).

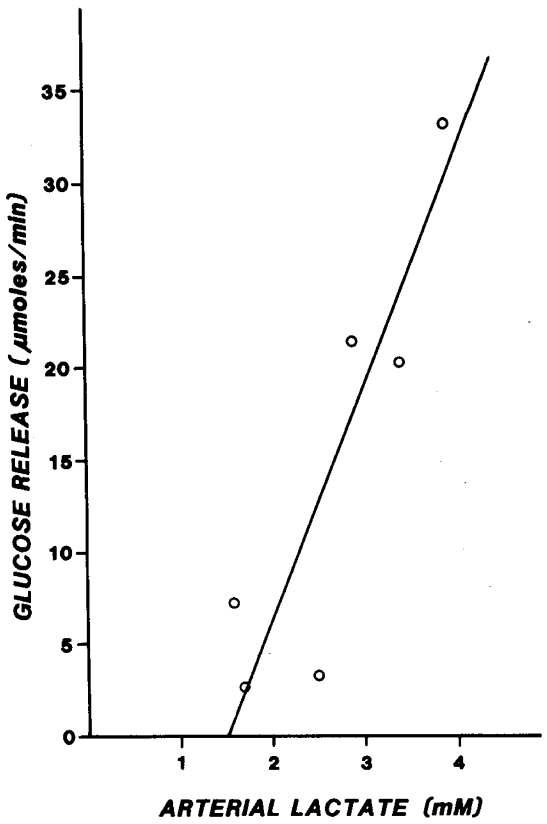

Fig. 3. Relationship of arterial lactate levels to splanchnic glucose release in baboon neonates ($r = 0.89$, $p < 0.05$).

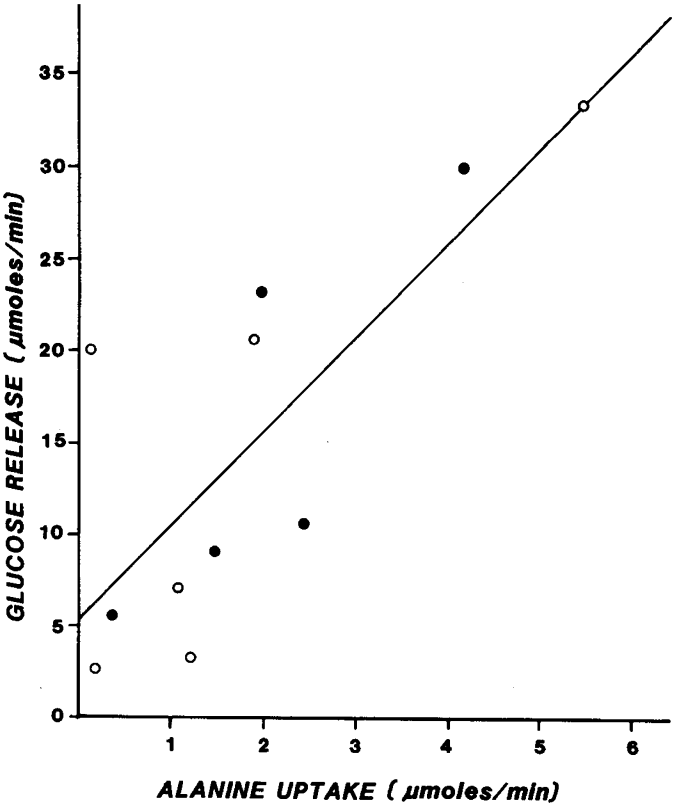

Fig. 4. Relationship of alanine uptake by the splanchnic bed to glucose release. O, neonates; ●, older infants ($r = 0.77$, $p < 0.01$ for both groups; $r = 0.84$ neonates, and $r = 0.75$, older infants; NS).

considered estimates, and are dependent upon determinations of plasma flow. Nonetheless, these estimates afford important clues concerning the nature of splanchnic energy exchange in the primate neonate and can be compared to data obtained in man.

Free fatty acids, which are important substrates for splanchnic energy needs in the adult (12), were not measured in this study. Therefore, the energy sources for the splanchnic bed cannot be fully quantitated. We may, however, examine splanchnic glucose production and concomitant uptake of gluconeogenic substrates in these fasted animals. Through direct hepatic vein catheterization, short-term fasted man has been estimated to produce between 2 and 4 mg/min·kg of glucose (5, 9, 23, 31). Glucose production in the adult subjected to prolonged fasting decreases to less than one-half of that in the postabsorptive state. Stable isotope mass spectroscopy tracer findings were in the same range (3.7–11.1 mg/min·kg in one study and were 4.0–4.9 mg/min·kg in another) (4, 15). In contrast, hepatic glucose production by the isolated human fetal liver (1) is two to four times greater than estimated splanchnic glucose production in adult fasting man. Our estimates of hepatic glucose release of 2.6 mg/min·kg (95% confidence limits, 0.6 to 5.0 mg/min·kg) in the older baboon infant are somewhat lower than the isotopic determinations of new glucose production in human infants. However, length of fasting and age of infant subjects may influence isotopically determined glucose production rates in the human neonate. It is likely, therefore, that the wide range of glucose release we have noted could be secondary not only to methodologic problems inherent in these determinations, but also to differences in nutritional status of these animals of various weights and birth histories. Certainly, the range of splanchnic glucose production rates in the fasting baboon neonates in our study approximate those previously reported in fasting adult man. These relatively low splanchnic glucose production rates compared to new glucose production rates determined in some human neonates in the postabsorptive state may reflect adaptation to fasting. Fur-

ther, we have reported that the mean renal contribution to glucose production in the baboon neonate is 1.8 mg/min·kg compared to 0.6 mg/min·kg in the older infant baboon (20). This suggests that glucose production by liver and kidney in the neonate is approximately 4.4 mg/min·kg and in the older infant is approximately 3.4 mg/min·kg. These values more closely approximate those reported using isotopic tracer techniques.

Some measured glucose release in these animals may reflect glycogenolysis rather than gluconeogenesis. Nonetheless, splanchnic uptake of gluconeogenic precursors and release of glucose, which is readily identified in these fasting, euglycemic infant primates suggests active gluconeogenesis. This adaptation to the fasting state is only a transient phenomenon. We have previously determined that fasting for more than 24 h may lead to marked and symptomatic hypoglycemia (19). Therefore, as in the human infant and child, the compensatory mechanisms that permit long-term euglycemic fasting in adult man are not fully developed in the infant of this primate species. Further, the substrates that contribute to hepatic glucose production in the fasting state seem to differ in their proportionate contribution in the neonatal baboon (Table 4) and adult man (8). Although estimation of substrate release and uptake rates based upon measurements of plasma flow may lead to substantial errors in the quantitation of substrate uptake and release, the estimated proportionate uptake and release of substrates in this study may be examined more closely. These determinations essentially negate the influence of plasma flow.

In the fasting newborn infant, gluconeogenic equivalents for pyruvate, alanine, and glycerol account for approximately 12% of glucose production. Lactate uptake is variable but could account for 89% of glucose production. Therefore, it is likely that lactate plays a larger precursor role in the neonate and that lactate taken up by the splanchnic bed may be substrate for other processes in addition to gluconeogenesis. In the older infant, total gluconeogenic equivalents identified as alanine and pyruvate uptake alone were 9% of glucose production. Glycerol uptake was not measured but may be large, as lactate uptake made up only 38.0% of gluconeogenic equivalents in these animals. Further, the role of glycogenolysis in glucose release in these animals was not assessed. In contrast to short-term fasted adult man, where alanine uptake may make up 25% of total gluconeogenic equivalents extracted by the splanchnic bed (8), alanine appeared to contribute relatively little to splanchnic gluconeogenesis in these animals. Alanine could account for only a small fraction of glucose production in the neonate and only slightly more in older infants. This suggests that changes in plasma alanine levels in fasting animals at birth and at 6 wk reflect changes in peripheral release of alanine rather than splanchnic utilization.

The larger proportion of glucose release which could be related to lactate uptake in the newborn may be secondary to elevated levels of available lactate. Certainly, similar to reports in adult man (7), we have identified a relationship between arterial plasma lactate levels and splanchnic lactate uptake, as well as a relationship between arterial lactate and glucose release. In previous studies of renal glucose production using the same methodology, glucose production could also be related to arterial lactate (20). It may be noted that, although in adult man lactate normally accounts for less than 50% of total gluconeogenic equivalents taken up by the splanchnic bed (9), studies of the neonates of several species (29) would tend to substantiate the primacy of lactate as a gluconeogenic precursor in early life. As we have noted in studies of lactate release from peripheral tissues of the baboon neonate, glucose recycling through lactate is an active mechanism in this model and in the young of other species (21).

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