Endogenous Glucose Production during Constant Glucose Infusion in the Newborn Lamb

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Summary

Prompt diminution of endogenous hepatic glucose production is characteristic of the mature (adult) response to exogenous glucose infusion. We have tested the validity of this hypothesis in the neonatal period in 26 unanesthetized mixed breed term lambs and for comparison in eight 4- to 5-month-old mixed breed sheep. After a 7-hr fast, basal plasma glucose, insulin, and glucagon concentrations were determined following which the term lambs received either no glucose or 5.7, 11.7, or 21.7 mg glucose/kg/min over a period of 6 hr, and the 5-month-old sheep received either none or 5.7 mg glucose/kg/min. Glucose turnover was determined by the prime-constant infusion technique of Steele using ³H₆ radiolabeled glucose during a 50-min turnover period which followed the 6-hr infusion of 0.45% saline or varying doses of glucose following the onset of fasting by 14 hr. Both newborn and adult animals maintained a constant plasma glucose concentration and glucose specific activity during the turnover period. Endogenous glucose production persisted in the term lamb until the exogenous glucose infusion reached the rate of 21.7 mg/kg/min. In contrast, the adult lambs reduced their endogenous glucose production with an exogenous glucose infusion rate of 5.7 mg/kg/min. At the time the endogenous glucose production rates were significantly reduced, the plasma insulin level in the newborn lamb was 5-fold greater than that of the adult sheep.

Under steady state conditions of plasma glucose concentration and glucose specific activity, our data suggest that there is imprecise control of endogenous glucose production in the newborn lamb in contrast to the older sheep of 4-5 months of age. The absence of precise control may be due to decreased hepatic sensitivity for insulin.

In the adult, when glucose is infused at a rate equal to or greater than endogenous glucose output, endogenous glucose production will be curtailed promptly as a result of precise hepatic control of glucose homeostasis (5, 15, 16, 18). If the glucose infusion rate and decreased hepatic output are balanced and peripheral utilization remains unchanged, plasma glucose concentration will be constant.

Varma *et al.* (21) infused the newborn pup and adult dog with glucose estimated to be equal to or greater than the endogenous glucose production rate. The newborn pup failed to diminish endogenous glucose production and attain an equilibrium (steady state), but rather evidenced a rise in plasma glucose concentration over the 2-hr duration of the study with a nonsteady state. The adult, in contrast, reversed an initial rise in plasma glucose concentration and established a new equilibrium within 90 min of exogenous glucose infusion. It was speculated that this difference in neonatal and adult responses to exogenous glucose infusion was due to decreased tissue insulin sensitivity in the neonatal subjects.

To explore this hypothesis, varying concentrations of glucose were infused constantly in a newborn or young adult sheep for a sufficient time to produce a stable equilibrium (steady state) of

the plasma glucose concentration. These studies were initiated to ascertain the extent to which endogenous glucose production is diminished under steady state conditions of exogenous glucose infusion. Thus plasma glucose, insulin, glucagon, and glucose specific activity were determined and endogenous glucose production was derived for the neonatal lamb. These results were compared to those obtained for young adult (4- 5-month-old) sheep. The newborn lamb and sheep were used since this species has been used extensively in studies of carbohydrate metabolism in the perinatal period (6, 7).

MATERIALS AND METHODS

Twenty-six mixed breed newborn lambs (age at time of study = 3.6 ± 0.3 days) (mean $\pm$ SEM) and eight 4- to 5-month-old mixed breed adult sheep were the subjects of this study. The mean lamb weight was 4.5 ± 0.3 kg and the weight of the young adult sheep was 24.8 ± 0.5 kg. The newborn lambs were allowed to deliver spontaneously and were fed *ad libitum* by their mother.

Seven hours prior to the study, the newborn animal was removed from its mother and fasted. Subsequently, the animal was lightly restrained and blindfolded, and under local anesthesia the internal carotid artery and external jugular vein were catheterized for blood sampling and infusion, respectively, with a no. 5 French polyethylene catheter (Sherwood Medical Industries, St. Louis, MO). One hour of stabilization was allowed to minimize reaction to the catheterization. Thereafter, blood samples were obtained for basal glucose and insulin determination every 10 min over a 30 min baseline period, as well as for plasma glucagon concentration, which was collected in Trasylol (1000 units/ml blood). Subsequently, during an infusion period lasting 6 hr, one group of seven control animals (age 2.9 ± 0.5 days and weight 4.2 ± 0.5 kg) was infused with 0.06 ml/kg/min of 0.45% NaCl. Another group of 11 animals (age 3.8 ± 0.5 days and weight 4.5 ± 0.3 kg) was infused with a similar volume of 10% glucose monohydrate at a rate of 5.7 mg glucose/kg/min. A third group of four animals (age 4.6 ± 0.5 days and weight 4.1 ± 1.0 kg) received 11.7 mg/kg/min glucose. A final group of four animals (age 4.6 ± 0.5 days and weight 4.6 ± 0.5 kg) received 21.7 mg glucose/kg/min. The age and weight of the four groups of animals were comparable. Blood samples were obtained for glucose and insulin determination at 30-min intervals throughout this infusion period, and at hourly intervals for glucagon determination.

After 6 hr, after the constant infusion of saline or glucose when a constant level of plasma glucose was achieved, a prime dose consisting of 50% of the total tracer of ³H₆ (25 μ Ci/kg) (New England Nuclear, Boston, MA) radiolabeled glucose was given, followed by a constant infusion of the remaining tracer over the ensuing 110 min. Utilization of this isotope has been noted to measure the least amount of recycling in tracer kinetic studies in rabbits and sheep (3, 12). After a 60-min equilibration period following the priming dose, blood samples for plasma glucose, insulin, and glucose specific activity determination were obtained at 10-min intervals from 60-110 min and for plasma glucagon at

the beginning and end of the turnover period. The steady state of tracer was maintained during the final 50 min of isotopic tracer infusion. The plasma glucose concentration as well as plasma glucose specific activity were constant during this period in which the glucose turnover was derived.

Eight 4- to 5-month-old sheep of comparable weight were fasted for a similar period of 7 hr and were studied in a similar manner except that they were allowed to remain standing during the study and were not blindfolded. Four (weight 24.1 ± 0.9 kg) received a continuous infusion of 0.45% NaCl and four (weight 25.4 ± 0.4 kg) received 5.7 mg glucose/kg/min.

Plasma glucose concentration was determined by the glucose oxidase method on glucose analyzer (Yellow Spring Instrument Co., Yellow Springs, OH), insulin by double antibody radioimmunoassay by a modification of the method of Hales and Randle (9), and glucagon by a modification of the method of Faloona and Unger (4) using the K-30 antibody. All analyses were performed in duplicate. Glucose assay varied up to $\pm 2\%$, the insulin assay varied between $\pm 2\%$ at $10 \mu\text{U/ml}$ and $\pm 5\%$ at $80 \mu\text{U/ml}$, and the glucagon assay varied between $\pm 5\%$ between 125 and 1000 pg/ml .

Two hundred-microliter samples of plasma obtained for the turnover studies were deproteinized with equal volumes of 0.3 N barium hydroxide and 5% zinc sulfate. The pellet was washed three times with $200 \mu\text{l}$ distilled water. The supernate was then deionized using an ion exchange Pasteur pipette column which incorporated 1.5 cm of cation exchange resin, Dowex 50(H^+) (Sigma Chemical Co., St. Louis, MO), and 3 cm of the anion exchange resin, Duolite A-4(OH^-) (Diamond Shamrock Chemical Co., Redwood City, CA) after the method of Herrera *et al.* (10). Subsequently, because of unavailability of Duolite A-4(OH^-), Dowex 1(Cl^-) was used after the method of Vidnes (22). The effluent was then lyophilized and the residual powder was mixed with $100 \mu\text{l}$ water and 10 ml Aquasol and counted on a Packard dual channel liquid scintillation spectrometer (Packard Instrument Co., Inc., Downers Grove, IL).

The calculation used to derive glucose produced was as follows:

$$R_A = \frac{R_I^*}{Wt \times (G^*/G)}$$

The rate of appearance (R_A) was assumed to be equal to the rate of production under steady state conditions. The equation utilized assumes that the rate of appearance (R_A) is equal to the rate of infusion (R_I^*) in counts/min divided by the weight of the animal (Wt) in kg times the specific activity of plasma glucose (G^*/G) in counts per min per mg glucose (19). Six values of glucose specific activity (usually within $\pm 5\%$ range) were averaged to determine the mean glucose specific activity of the turnover period.

Unpaired *t*-tests were used for statistical analyses.

RESULTS

Figure 1 shows that in the newborn lamb, baseline plasma glucose values were similar in all groups prior to the onset of glucose infusion. The neonatal lambs, receiving no glucose, had a plasma glucose concentration averaging $122 \pm 23 \text{ mg/dl}$ and varying $\pm 4\%$ through 100 min of the turnover period. Glucose infusion resulted in a steady rise in plasma glucose concentration which stabilized after 120 min of infusion and was maintained with a $\pm 4\%$ range throughout the turnover period. There was a significant 2- to 4-fold increase in plasma glucose concentration during the turnover period noted when either 11.7, or 21.7 mg/kg/min glucose was infused, respectively, in comparison to when no glucose or 5.7 mg/kg/min glucose was administered ($P < 0.01$).

Figure 2 shows the plasma insulin values of the newborn lambs. The baseline plasma insulin of all lambs averaged $27 \pm 7 \mu\text{U/ml}$ and remained stable when 0.45% saline was infused during the turnover period. When 5.7 mg glucose/kg/min was infused, the plasma insulin concentration remained similar to that noted in the 0.45% saline infused (control) animals even though a rise in plasma glucose occurred (Fig. 1). Infusion of 11.7 mg

glucose/kg/min produced a rise of insulin which was statistically different from the plasma insulin concentration noted in animals receiving only 0.45% saline during the turnover period at all time points except one (at 70 min) ($P < 0.02$). When 21.7 mg glucose/kg/min was infused, wide variability in plasma insulin concentration was observed but the mean increment at each period of sampling during the turnover period was significantly higher than in the 0.45% saline-infused lambs ($P < 0.05$).

The eight adult sheep evidenced uniformly higher average baseline plasma glucose concentration in comparison to the neonatal lambs (Fig. 3). The four animals receiving 0.45% saline and the four sheep receiving 5.7 mg/kg/min of exogenously administered glucose subsequently stabilized and had a stable steady state plasma glucose concentration throughout the turnover period.

The 5-month-old animals receiving 0.45% saline infusion evidenced an average plasma glucose concentration of $76 \pm 6 \text{ mg/dl}$ which resulted in a plasma insulin concentration of $15 \pm 2 \mu\text{U/ml}$. In contrast, infusion of 5.7 mg glucose/kg/min produced a significant rise in plasma glucose concentration during the turnover period of $174 \pm 29 \text{ mg/dl}$ ($P < 0.02$), resulting in a significant elevation of plasma insulin concentration to $56 \pm 8 \mu\text{U/ml}$ ($P < 0.01$).

PLASMA GLUCOSE (mg/dl)

Fig. 1. Plasma glucose values in the newborn lamb after exogenous glucose infusion.

PLASMA INSULIN ($\mu\text{U/ml}$)

Fig. 2. Corresponding plasma insulin values in the newborn lamb after exogenous glucose infusion.

Fig. 3. Plasma glucose values (lower panel) and plasma insulin values (upper panel) in the 4- to 5-month-old sheep after exogenous glucose infusion.

Fig. 4. Plasma glucagon values in the newborn lamb (upper panel) and in the 4- to 5-month-old sheep (lower panel) after exogenous glucose infusion.

Figure 4 shows the plasma glucagon values of the newborn lambs and adult sheep. The newborn lambs evidenced similar plasma glucagon levels during the baseline period which remained stable throughout both the infusion and turnover periods irrespective of whether 0, 5.7 mg, or 11.7 mg glucose/kg/min was infused. (Because of technical difficulties, plasma glucagon was not measured in animals receiving 21.7 mg glucose/kg/min.) The adult sheep correspondingly showed similar values for plasma glucagon in animals receiving 0.45% saline or 5.7 mg glucose/kg/min except at 360 min of the infusion period and 60 min of the turnover period when the animals receiving the glucose infusion evidenced higher values ($P < 0.05$).

Table 1 summarizes the results of plasma glucose, plasma insulin, plasma glucagon, and endogenous glucose production in both the newborn and adult animals during the turnover period. In the newborn lamb with increasing concentrations of glucose infusion, the plasma glucose level rose proportionately, as expected. The plasma insulin levels also increased proportionately with increasing glucose concentration but were significantly higher at 11.7 and 21.7 mg/kg/min of exogenous glucose infusion. Endogenous glucose production rates remained unchanged at 0, 5.7, and 11.7 mg/kg/min of exogenous glucose infusion, but significantly reduced to 0.6 ± 1.1 mg/kg/min when exogenous glucose infusion reached 21.7 mg/kg/min ($P < 0.02$). In the adult sheep, 5.7 mg/kg/min exogenous glucose infusion resulted in a significant reduction in endogenous glucose production to 0.9 ± 0.3 mg/kg/min (23). There were no significant differences in plasma glucagon concentration in either newborn or adult sheep at any rate of exogenous glucose infusion.

DISCUSSION

The primary objective of this study was to determine whether precise control of endogenous glucose production was present in the neonatal period using a newborn lamb model. These studies have focused on the relationship between plasma glucose and plasma insulin concentration only during the final 50 min of the study (last portion of the turnover period) when endogenous glucose production could be derived under steady state conditions of constant plasma glucose concentration and constant glucose specific activity. We have not compared values for concentration of plasma glucose or plasma insulin in the turnover period with values obtained either in the baseline period or the infusion period for a number of reasons. First, the higher initial plasma glucose and insulin values of the adult (control) sheep who received only 0.45% saline were probably due to stress during the catheterization and baseline period, since both plasma glucose and insulin values fell subsequently. Because of this undefined "stress," intrasubject comparisons noted under steady state conditions at the end of the study with those obtained early in the protocol are difficult to

Table 1. Plasma glucose, insulin, glucagon concentrations and endogenous glucose production in study subjects at various glucose infusions during turnover period¹

Subjects	n	Glucose infusion rate, mg/kg/min	Plasma glucose, mg/dl ²	Plasma insulin, μU/ml ²	Plasma glucagon, pg/ml ²	Endogenous glucose production, mg/kg/min ²
Newborn lamb	7	0	122 ± 23	25 ± 3	300 ± 41 ³	7.4 ± 1.1
	11	5.7	182 ± 18	31 ± 6	283 ± 56 ³	4.8 ± 0.7
	4	11.7	238 ± 32 ⁴	70 ± 16 ⁵	265 ± 77	6.4 ± 1.7
	4	21.7	464 ± 23 ⁴	270 ± 108 ⁶		0.6 ± 1.1 ⁵
Adult sheep	4	0	76 ± 6	15 ± 2	254 ± 25	2.8 ± 0.2
	4	5.7	174 ± 29 ⁵	56 ± 8 ⁴	309 ± 20	0.9 ± 0.3 ⁵

¹ Unpaired *t*-tests were performed between each infusion group and the 0.45% saline (0 glucose) group.

² Mean ± SEM.

³ Because of technical difficulties, 3 of 7 (0 glucose infused) and 5 of 11 (6 mg glucose/kg/min infused) samples were unavailable for analysis.

⁴ $P < 0.01$.

⁵ $P < 0.02$.

⁶ $P < 0.05$.

interpret. A similar situation of lesser magnitude may have existed with the newborn sheep, noted by the variable initial baseline plasma insulin values of those who were to receive 0.45% saline infusion. Secondly, interpretation of comparisons of the steady state values of the turnover period with the nonsteady state conditions of the infusion period when the animals were adjusting to the various exogenous infusions is similarly difficult.

Although any recycling of the label would result in diminution of apparent new glucose produced, in the newborn lamb endogenous glucose production was 7.4 ± 1.1 mg/kg/min in animals receiving 0.45% saline infusion. This elevated level of endogenous glucose production in the neonate (in contrast to the adult) has previously been shown in the puppy by Kornhauser *et al.* (13), in the term rhesus monkey newborn by Sherwood *et al.* (17), and in the human by Bier *et al.* (2). In contrast, the 4- to 5-month-old sheep evidenced an endogenous glucose production of 2.8 ± 0.2 mg/kg/min which is comparable to values noted for the adult dog by Steele (20) and for man by Madison (16). Similarity is noted in the data for both neonatal and adult subjects in spite of differences in dietary substrate, gut absorption, and hepatic metabolism in the various species.

Incremental differences in glucose concentration dictate pancreatic Beta cell response (8). Plasma glucose and, therefore, plasma insulin concentrations in the newborn lambs were not significantly different in those animals receiving 5.7 mg glucose/kg/min in comparison to the newborn lambs receiving 0.45% saline. In contrast, the adult sheep evidenced a significant increase in plasma glucose concentration (174 ± 29 mg/dl) in the animals receiving 5.7 mg/kg/min of exogenous glucose when compared to the adult sheep infused with 0.45% saline (76 ± 6) ($P < 0.02$). As such, a significant rise in plasma insulin concentration was seen in the adults receiving exogenous glucose administration in contrast to the controls (56 ± 8 vs. 15 ± 2) ($P < 0.01$). When the plasma glucose concentration in the neonatal lambs rose significantly to 238 ± 32 mg/dl in response to an infusion of 11.7 mg glucose/kg/min ($P < 0.01$), a significant elevation in plasma insulin concentration was also seen (70 ± 16 vs. 25 ± 3) ($P < 0.02$). Thus, pancreatic β cell response to plasma glucose concentration in the neonatal animals appears comparable to that noted in the older adult animals.

Hetenyi *et al.* (11) have recently reported that in the newborn puppy (in contrast to the adult), 1) fasting resulted in a decrease in plasma glucagon and 2) insulin induced hypoglycemia resulted in failure to increase plasma glucagon concentration. Bassett (1) infused 8 mg glucose/kg/min into adult sheep and found failure of significant diminution of plasma glucagon concentration over 3 hr even though a marked increase in plasma glucose concentration occurred. In our studies in the newborn sheep, we have similarly found that hyperglycemia caused by chronic glucose infusion did not result in diminution in plasma glucagon even though there were significant increases in plasma glucose and insulin concentration in both newborn and adult animals. Thus pancreatic α cell secretion did not seem to respond to chronic exogenous administration of glucose in either the newborn or adult animal.

Because of placement of our catheters, we did not measure endogenous hepatic glucose production directly. The values obtained for endogenous glucose production represent not only hepatic glucose production but other sites, such as the kidney, as well. Levitsky *et al.* (14) have shown that renal glucose release may account for up to 33% of the total endogenous glucose production in the fasting baboon neonate. Thus, the liver is probably the primary but not the only site of endogenous glucose production in the fasting neonate.

Over 30 years ago Soskin *et al.* (18) originally proposed the hypothesis of auto-regulation of hepatic glucose production by the magnitude of glucose delivery to the liver. The adult control of glucose homeostasis is precise in that endogenous hepatic glucose production diminishes promptly when exogenous glucose administration equals or exceeds the endogenous hepatic glucose output. This has been demonstrated in the adult by Madison (16) using

hepatic vein catheterization and by Steele (20) using isotope dilution of radio-labelled glucose. More recently Varma *et al.* (21) compared endogenous glucose production in the beagle pup to that in the adult dog. Under conditions of exogenous glucose infusion, endogenous glucose production was diminished in four of five adult dogs studied.

Hepatic unresponsiveness to insulin may be a major mechanism explaining the inefficiency in glucose homeostasis in the neonate. When the rate of exogenous glucose infusion was approximately doubled in comparison to endogenous glucose production in both groups of animals, the neonatal lamb was unable to diminish endogenous glucose production as the adult was able to do. In fact, endogenous glucose output was decreased in the newborn only in response to an exogenous glucose infusion three times the control (0.45% saline) value. The concept of hepatic insensitivity is emphasized when one contrasts the plasma insulin concentration required to diminish endogenous glucose production in the neonatal model in comparison to that required in the older animal. In the former, endogenous hepatic glucose response was significantly diminished when a peripheral plasma insulin concentration of 270 ± 108 μ U/ml was achieved by the β cell of the pancreas. Significant diminution in endogenous hepatic glucose response, however, occurred in the adult when plasma insulin concentration reached 56 ± 8 μ U/ml. This hepatic insensitivity to insulin may be an important mechanism responsible for the persistence of endogenous glucose production when glucose is infused in the neonatal period.

CONCLUSION

Our studies have shown that a steady state of plasma glucose concentration is possible in the neonate and young adult lamb in response to an exogenous glucose infusion. Using the prime plus constant infusion technique of Steele with tritiated glucose, one can calculate endogenous glucose production in response to exogenous glucose infusion. While precise control of endogenous glucose response is characteristic of the mature (adult) animal, the neonate evidenced inability to suppress endogenous glucose production at moderate glucose levels. This immaturity could be explained by hepatic unresponsiveness to insulin (in contrast to the adult).

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 23. A fifth animal evidenced endogenous glucose production of 5.10 mg/kg/min which was nearly twice the endogenous glucose output in the animal receiving no exogenous glucose and even exceeded the values for the infused group as well. Except for the possibility of stress in this animal at the time of turnover, this is unexplained. This animal has not been included in the detailed analysis.
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