The Contribution of Glucose to Neonatal Glucose Homeostasis in the Lamb

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A multiplicity of substrates and hormones interact to influence neonatal glucose homeostasis. Based on prior studies in our laboratory, we hypothesized that glucose alone does not tightly control neonatal glucose homeostasis. Fifteen spontaneously delivered, mixed-breed term lambs, weighing 4.7 ± 0.9 kg (mean ± SD) were studied at 4.7 ± 0.6 days after birth following administration of 100 μCi D[6,6-$^3H_2$] glucose in 0.9% NaCl by the prime plus constant infusion technique to measure glucose production. After a baseline period, five lambs received 8.5 mg · kg^{-1} · min^{-1} glucose in combination with the following to isolate the contribution of glucose: somatostatin to block insulin, glucagon, and growth hormone release; metyrapone to block cortisol release; phentolamine to block α-adrenergic release; and propranolol to block β-adrenergic release (glucose + blockade). Five lambs received the above without the glucose infusion (blockade). Five lambs continued to receive 0.9% NaCl alone as the diluent for the isotopic tracer throughout the study (control). The glucose + blockade group had a significant increase in plasma glucose ($P < .0001$) and a significant increase in total glucose appearance ($P < .0001$) compared with both the blockade and control groups. Under conditions of glucose infusion at a rate 49% greater than the basal rate, the endogenous glucose production rate persisted such that there was only an evanescent decrease compared with that of the control group, which was not statistically different over time. As a substrate, glucose does not tightly control neonatal glucose homeostasis.

AS HAS BEEN DISCUSSED elsewhere, the neonate is in a transitional state of glucose homeostasis. While the fetus is completely dependent on the mother for glucose (nutrient) transfer across the placenta, the nonpregnant, nondiabetic adult is independent.[1] The neonate must obtain substrate, especially carbohydrate for energy and growth, to maintain a balance between glucose deficiency and excess.

As the major glucoregulatory hormone, insulin suppresses glucose production and accelerates glucose utilization. Insulin appears to be important in the hormonal control of neonatal glucose homeostasis, although in most published series adult-like control of glucose homeostasis is not evident in the neonate.[2-6] It is apparent that maturation of neonatal glucose homeostasis results from a balance between insulin action, the developing counterregulatory hormones, and substrate availability. Investigations in this area have focused either on insulin action or on the counterregulatory hormones rather than on substrate availability.[7-10]

Sixty years ago, Soskin et al[11] hypothesized that the primary mechanism regulating hepatic glucose output was related to the ability of the liver to adjust its glucose production in response to changes in the circulating concentration of glucose. This process has been called hepatic autoregulation when it has been studied in the absence of changes in the various hormones and neural regulatory influences. This phenomenon has been considered important in the metabolism of glucose in the adult, as manifested by the number of studies in which it has been evaluated.[12-16] However, to our knowledge, there have been no parallel studies of its presence (ie, importance) in the neonatal period. As part of our continuing evaluation of the ontogeny of neonatal glucose homeostasis, we used a well-described lamb model to isolate the effect(s) of glucose on neonatal glucose homeostasis. We administered a glucose infusion during concomitant blockade of insulin, the counterregulatory hormones, and specific neural regulatory influences important in glucose homeostasis, and measured the resultant rate of glucose appearance following "isolation" of glucose.

MATERIALS AND METHODS

Fifteen mixed-breed neonatal lambs weighing 4.7 ± 0.9 kg (mean ± SD) were studied at 4.7 ± 0.6 days after birth. The ewes were allowed to deliver spontaneously, and the lambs were fed ad libitum by their mother until approximately 12 hours prestudy. The catheterization protocol has previously been described in detail.[8,9,14] Essentially, the lamb was removed from its mother and fasted. It was considered a nonruminant since it had not been weaned. At the time of catheterization, the animal was lightly restrained and blindfolded. Under local anesthesia with 1% Lidocaine (Elkins-Sinn, Cherry Hill, NJ), the internal carotid artery and external jugular vein were catheterized for blood sampling and infusion, respectively.

After 1 hour of stabilization following the catheterization procedure, the lamb received 100 μCi · kg^{-1} D-[6,6-$^3H_2$]glucose in 0.9% NaCl at 0.06 ml · kg^{-1} · min^{-1} by the prime-constant infusion technique of Steele for 150 minutes. During the next 30 minutes, baseline samples were drawn every 10 minutes for determination of plasma concentrations of glucose, insulin, glucagon, growth hormone, cortisol, glucose specific activity, and blood gases, for a total of four samples. Corresponding measurements of heart rate and systolic and diastolic blood pressure were recorded. Subsequently, blood samples were taken and measurements recorded every 20 minutes during the experimental period when one of the following three groupings of infusates were administered: (1) five lambs received 8.5 mg · kg^{-1} · min^{-1} glucose in combination with the following to isolate the contribution of glucose: 1.0 μg · kg^{-1} · min^{-1} somatostatin (Sigma, St Louis, MO) to block insulin, glucagon, and growth hormone release; 0.3 mg · kg^{-1} · min^{-1} metyrapone (Sigma) to block cortisol release; 0.5 mg · kg^{-1} · min^{-1} phentolamine (Ciba-Geigy, Summit, NJ) to block α-adrenergic release; and 1.1 mg · kg^{-1} · min^{-1} propranolol (SoloPAK Laboratories, Elk Grove Village, IL) to block β-adrenergic release (glucose + blockade); (2) five lambs received the above without the addition of glucose to the infusate (blockade); and (3) five lambs continued to receive 0.9% NaCl alone as the diluent for the isotopic tracer throughout the study (control). The administered doses of the infusates were similar to those previously

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used in studies in this lamb model or modified from those used in studies in men on a per-kilogram basis.[9]

The plasma glucose concentration was measured on a YSI 2700 Select Biochemistry Analyzer (YSI, Yellow Springs, OH). The insulin level was measured by a single-antibody radioimmunoassay (Coat-A-Count Insulin; Diagnostic Products, Los Angeles, CA). The glucagon concentration was measured by a double-antibody radioimmunoassay (ICN Pharmaceuticals, Costa Mesa, CA). Cortisol was determined by a single-antibody radioimmunoassay (Clinical Assays GammaCoat Cortisol ^{125}I RIA Kit; Incstar, Stillwater, MN). The growth hormone level was measured by a single-antibody radioimmunoassay (National Hormone and Pituitary Program, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD). Blood gases were measured on a Ciba-Corning 238 pH/blood gas analyzer (Ciba-Corning, Norwood, MA). The heart rate and systolic and diastolic blood pressure were recorded on a Corometrics 556 Monitor (Corometrics Medical Systems, Wallingford, CT).

The procedure for determination of glucose specific activity has previously been published.[7-9] From the determination of glucose specific activity, the glucose appearance rate was calculated according to the equations of Steele et al.[17] By convention, the total glucose appearance rate is equal to the endogenous glucose production rate plus the exogenously infused glucose rate. The latter was subtracted from the total glucose appearance rate to calculate the endogenous glucose production rate. Unlike other studies from our laboratory, non–steady-state calculations have been used because of the incremental changes that occurred during each specific infusion period.[17,18]

To compare data between groups for each specific parameter over the 2-hour time course of the perturbation, statistical analysis was made by the rigorous SAS Proc Mixed Design using a two-stage model (SAS Institute, Cary, NC). Data obtained during the baseline period were averaged to determine the mean value for each basal concentration (ie, blood glucose) or measurement (ie, heart rate) for each group. Cluster analysis of the specific concentration or measurement for each animal provided a regression for the specific parameter being evaluated over the 2-hour period of the experimental perturbation (ie, plasma glucose concentration or heart rate per minute, etc.). Subsequently, the specific individual regression coefficients were combined to calculate a group regression coefficient for each specific parameter. Thus, the analysis first compared basal concentrations between groups, then the changes within groups throughout the experimental period, and then the changes between groups throughout the experimental period. The ultimate comparison was between groups over time relative to the initial respective basal concentration or rate. Following comparison of the three groups, a Bonferroni correction factor was calculated to correct for sample size. Significance was set at a P level of less than .017.

RESULTS

Figure 1A depicts the blood glucose concentration over time through the 2-hour administration period by group. There were no significant differences between the mean blood glucose concentrations of the groups during the basal period. Over time, there was a significant increase in blood glucose in the glucose + blockade group versus the control group ($P < .0001$) and a significant increase in blood glucose in the blockade group versus the control group ($P < .0008$). The blood glucose concentration of the glucose + blockade group was significantly increased compared against that of the blockade group ($P < .0001$).

Figure 1B depicts the total glucose appearance rate over time through the 2-hour period of administration by group. There were no physiological differences between the mean glucose appearance rates of the groups, which were 27.48 ± 2.28 to 38.30 ± 2.16 μmol · kg^{-1} · min^{-1} (4.95 ± 0.41 to 6.90 ± 0.39 mg · kg^{-1} · min^{-1}, mean ± SE) during the basal period. Over time, there was a significant increase of the glucose appearance rate in the glucose + blockade group and the blockade group versus the control group ($P < .0001$). The glucose appearance rate was significantly increased in the glucose + blockade group compared with the blockade group ($P < .0001$).

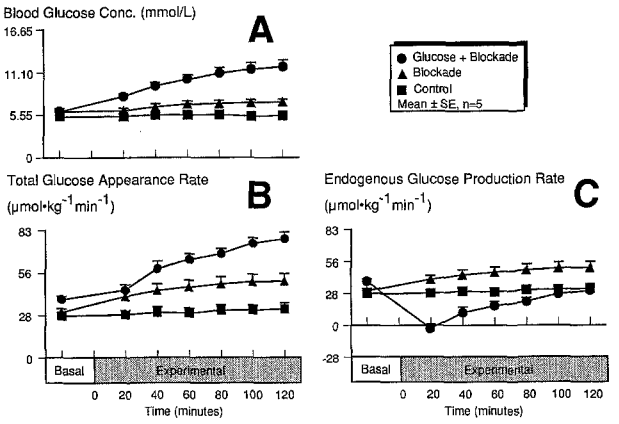

Fig 1. (A) Blood glucose concentration over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (B) Total glucose production rate over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (C) Endogenous glucose production rate over time from the means of the basal period through the 2-hour administration period of the various infusions by group.

Figure 1C depicts the endogenous glucose production rate over time through the 2-hour period of administration by group. There were no physiological differences between the mean glucose production rates of the groups, which were 27.48 ± 2.28 to 38.30 ± 2.16 μmol · kg^{-1} · min^{-1} (4.95 ± 0.41 to 6.90 ± 0.39 mg · kg^{-1} · min^{-1}) during the basal period. There was a decline in the endogenous glucose production rate of the glucose + blockade group following initiation of the infusion, but there was no significant difference for the glucose + blockade group compared with the blockade group or control group over time. There was a significant increase of the glucose production rate of the blockade group compared with the control group ($P < .0001$).

Figure 2A depicts the plasma insulin concentration over time through the 2-hour period of administration by group. There were no significant differences between the mean plasma insulin concentrations of the groups during the basal period. Over time, there was a significant increase in the plasma insulin concentration of the glucose + blockade group versus the control group ($P < .0107$) and a significant decrease of plasma insulin in the blockade group versus the control group ($P < .0022$). The plasma insulin concentration was significantly increased in the glucose + blockade group compared with the blockade group ($P < .0002$).

Figure 2B depicts the plasma glucagon concentration over time through the 2-hour period of administration by group. There were no significant differences between the mean plasma glucagon concentrations of the groups during the basal period. Over time, there was no significant decrease in the plasma

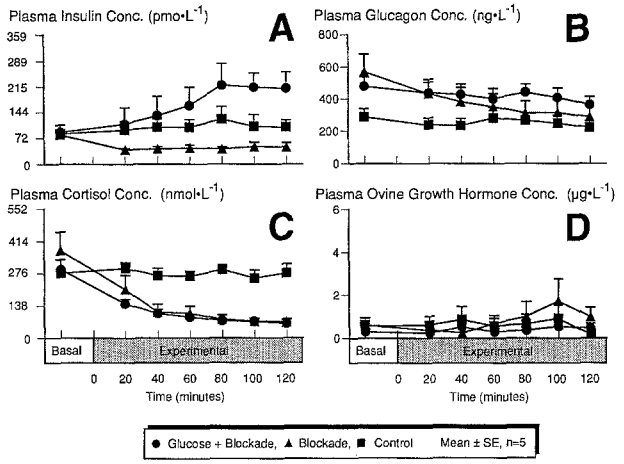

Fig 2. (A) Plasma insulin concentration over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (B) Plasma glucagon concentration over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (C) Plasma cortisol concentration over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (D) Plasma growth hormone concentration over time from the means of the basal period through the 2-hour administration period of the various infusions by group.

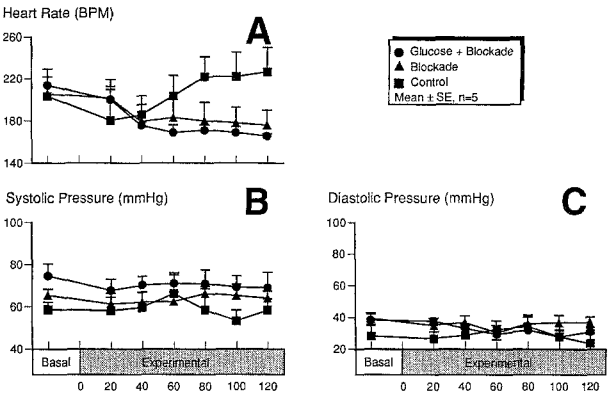

Fig 3. (A) Heart rate per minute over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (B) Systolic blood pressure over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (C) Diastolic blood pressure over time from the means of the basal period through the 2-hour administration period of the various infusions by group.

glucagon concentration of the glucose + blockade group versus the control group, but there was a significant decrease of plasma glucagon in the blockade group versus the control group ($P < .0001$). The plasma glucagon concentration was significantly decreased in the blockade group compared with the glucose + blockade group ($P < .0109$).

Figure 2C depicts the plasma cortisol concentration over time through the 2-hour period of administration by group. There were no significant differences between the mean plasma cortisol concentrations of the groups during the basal period. Over time, there was a significant decrease in the plasma cortisol concentration of the glucose + blockade group and blockade group compared with the control group ($P \leq .0032$). There was no significant difference in the plasma cortisol concentration of the glucose + blockade group versus the blockade group.

Figure 2D depicts the plasma growth hormone concentration over time through the 2-hour period of administration by group. There were no significant differences between the mean plasma growth hormone concentrations of the groups during the basal period or throughout the period of the various infusions.

Figure 3A depicts the heart rate over time through the 2-hour period of administration by group. There were no significant differences between the mean heart rates of the groups during the basal period. Over time, there was a significant decrease in the heart rate of the glucose + blockade group and blockade group versus the control group ($P \leq .0010$). The heart rate of the glucose + blockade group was not significantly different from that of the blockade group.

Figure 3B depicts the systolic blood pressure over time through the 2-hour period of administration by group. There were no significant differences between the mean systolic blood pressures of the groups during the basal period or throughout the period of the various infusions.

Figure 3C depicts the diastolic blood pressure over time through the 2-hour period of administration by group. There were no significant differences between the mean diastolic blood pressures of the groups during the basal period or throughout the period of the various infusions.

Figure 4A depicts the pH over time through the 2-hour period of administration by group. There were no significant differences between the mean pH levels of the groups during the basal period or throughout the period of the various infusions for the glucose + blockade and blockade groups versus the control group. The pH of the blockade group was not physiologically higher than that of the glucose + blockade group.

Figure 4B depicts the pO_2 over time through the 2-hour period of administration by group. There was no significant difference between the pO_2 of the groups during the basal period or throughout the period of the various infusions.

Figure 4C depicts the pCO_2 over time through the 2-hour

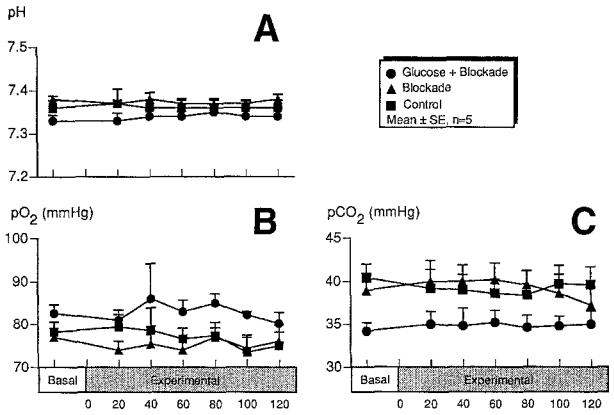

Fig 4. pH over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (B) pO_2 over time from the means of the basal period through the 2-hour administration period of the various infusions by group. (C) pCO_2 over time from the means of the basal period through the 2-hour administration period of the various infusions by group.

period of administration by group. There were no physiological differences between the pCO_2 of the groups during the basal period, which was 40 ± 2 to 34 ± 1 mm Hg. Over time, the pCO_2 of the blockade group was not physiologically decreased compared with the control group. The pCO_2 of the glucose + blockade group was not significantly different from that of the control group or the blockade group.

DISCUSSION

The primary objective of this study was to isolate the contribution of glucose from that of the various hormones and neural regulatory factors important in the ontogeny of neonatal glucose homeostasis. We chose to isolate the effect(s) of glucose to study the degree to which it influences neonatal glucose homeostasis.[11] This has not been studied in the neonatal period heretofore. We used the following: somatostatin, a known inhibitor of insulin, glucagon, and growth hormone; phentolamine, a known inhibitor of α-adrenergic agonists; propranolol, a known inhibitor of β-adrenergic agonists; and metyrapone, a known inhibitor of cortisol. This series of inhibitors, infused collectively with and without simultaneous administration of glucose at a rate of 8.5 $mg \cdot kg^{-1} \cdot min^{-1}$, isolated the contribution of glucose to neonatal glucose homeostasis.

The lamb has been used to study glucose kinetics in the neonatal period.[7-9,14] It was made postabsorptive for a period of 12 hours. This length of time resulted in a fasted state because the lamb is not considered a true ruminant until it is weaned. The stability of this lamb model was confirmed by the general constancy of data relative to the plasma glucose concentration, plasma insulin concentration, various contra-insulin hormones, as well as heart rate, systolic and diastolic blood pressure, and blood gases in the control group. The effect of propranolol was established by the decline in heart rate in the two groups of lambs that received the β-agonist inhibitor, and is the explanation for why the control group evidenced a general increase in heart rate compared with the other two groups over time during the experimental period. As would be expected, the pH of the groups was uniform compared with the inherent variability of pO_2 and pCO_2 measurements. Despite some statistically significant differences in the pH and pCO_2 measurements between groups, we suggest that these values were all in a physiologically normal range over the time course of the study.

We recognize that our peripherally placed catheters (ie, the internal carotid artery was used for sampling) did not allow for direct measurement of substrates or hormones secreted from the pancreas and/or the liver. However, since they are well known to exert specific predictable effects on the rate of glucose appearance (turnover), the measurement of endogenous glucose production has been used as the marker for the differential effect of glucose on neonatal glucose kinetics.[7-9,14]

Three previous studies have used somatostatin administration to evaluate glucose homeostasis in the neonatal period. Hetenyi et al[19] studied the newborn puppy, and Sperling et al[20] and Cowett and Tenenbaum[9] studied the newborn lamb. Hetenyi et al[19] noted a decrease in the plasma insulin concentration comparable to when the puppy was infused with saline alone, but failed to show a decrease in the plasma glucagon concentration. Sperling et al[20] noted a decrease in plasma glucagon but a variable response in plasma insulin. Cowett and Tenenbaum[9] noted a decrease in plasma insulin but no change in the plasma glucagon concentration. The reason(s) for these variable responses are not apparent. However, Hetenyi et al[19] suggested that in the newborn puppy, α and β cells are less responsive to somatostatin compared with the adult. The degree to which somatostatin depressed plasma insulin and glucagon concentrations in the current data set was parallel to the degree previously shown by our laboratory,[9] as well as by others in the adult.[12] For example, the increase in plasma insulin during the glucose + blockade infusion compared with blockade alone indicates that somatostatin did not completely inhibit insulin secretion in response to a glucose infusion. In fact, a review of those specific data would suggest that it took a period of at least 1 hour (of a total 2-hour infusion) for glucose to cause a significant elevation in the plasma insulin concentration. Because somatostatin does not have an absolute inhibitory effect on the secretion of insulin, glucagon, and growth hormone, these data must of necessity be compared against data previously generated in this laboratory evaluating the effect(s) of specific glucose infusion on neonatal glucose homeostasis.

During kinetic studies using stable and/or radioactive isotope methodology, glucose infusion, glucose absorbed from the gastrointestinal tract, glycogenolysis, and gluconeogenesis may collectively contribute to the rate of glucose appearance. In effect, the increase in the total glucose production rate in the glucose + blockade group was related specifically to the infusion of glucose in comparison to the blockade group. Only the latter two variables (ie, glycogenolysis and gluconeogenesis) reflect the endogenous glucose production rate. Hormones and substrates that are known to play a role in suppressing endogenous glucose production include insulin and glucose, respectively.[2,4,21] The initial decline in the endogenous glucose production rate over the first 20 minutes and then subsequent increase over the next 100 minutes of the experimental period can be interpreted to indicate that glucose initially had only an evanescent suppressive effect that was not sustainable over time.

The utilization of the hyperinsulinemic-euglycemic clamp technique in the human neonate has recently been reported.[22] Persistent glucose production was apparent during a wide range of insulin infusion rates. Endogenous glucose production was sensitive to a low insulin concentration, reached a plateau quickly, and then became nonresponsive to higher insulin concentrations. Endogenous glucose production was reduced by about 50% at a plasma insulin concentration up to 89 $mU \cdot mL^{-1}$. In another series, this parallel response existed in the term and preterm neonate early in the neonatal period and in the preterm neonate at the end of the neonatal period.[23] We have previously concluded that insulin only partially suppresses the endogenous glucose production rate in the neonatal period, and this was reaffirmed by the data presented here. In the glucose + blockade group, an elevation of plasma insulin was apparent in response to the infusion of glucose despite concurrent administration of somatostatin. In that group, the endogenous glucose production rate was not significantly different from that of the control group, indicating that either insulin did not diminish the

endogenous production of glucose and/or the infused glucose was unable to diminish it over the total experimental period.

The dichotomy in the neonatal literature relative to the responsiveness of endogenous glucose production to glucose, and correspondingly, to the rate of glucose infusion, is apparent from a review of the literature.[1] We and others have previously demonstrated that persistent glucose production exists during glucose infusion at rates similar to or slightly above the basal glucose production rate in the neonate.[2,4,5] Other investigators have suggested that the plasma glucose concentration itself has an important regulatory effect on the rate of endogenous glucose production.[3,4,24,25] When the results of glucose kinetics studies in three groups of neonates (ie, appropriate for gestational age, small for gestational age, and low–birth weight preterm neonate) were combined, Kalhan et al[4] reported a linear and negative correlation between the plasma glucose concentration and endogenous glucose production. Complete suppression of glucose production was not achieved in that study. Hertz et al[3] showed a similar correlation in the very–low-birth weight neonate. They reported a reduction in endogenous glucose production at moderate glucose infusion rates, but complete suppression of glucose production was only achieved at a relatively high glucose infusion rate and plasma glucose concentration of 53 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and 7.5 mmol/L (9.5 $mg \cdot kg^{-1} \cdot min^{-1}$ and 136 mg/dL), respectively. Zarlengo et al[25] used the hyperglycemic clamp technique in a group of low–birth weight neonates to evaluate this issue. Although glycemic concentrations among the neonates were not closely matched in their clamp study, the investigators reported complete suppression of glucose production in all neonates at a plasma glucose concentration of at least 4.2 mmol/L ($\geq$75 mg/dL) with an average glucose infusion rate of 48 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ ($8.7 mg \cdot kg^{-1} \cdot min^{-1}$). Although there are differences among these data sets in the weight, gestational age, glucose concentration, and glucose infusion rate of the populations studied, there is general agreement that complete suppression of glucose production can only be achieved at a plasma glucose concentration and a glucose infusion rate greater than the known basal values for the neonate. Developmentally, this is in marked contrast with the adult, in whom glucose production can be suppressed when glucose is infused at a rate equal to or slightly greater than the basal endogenous glucose production.[6]

In essence, the data reported in this study specifically address the issue of glucose as a substrate influencing glucose production. Compared with controls, the lambs receiving glucose + blockade had an increase in plasma glucose and an increase in total glucose appearance but no sustained decrease in endogenous glucose production. Initially, there was a decrease immediately following the glucose infusion. However, over the course of the glucose infusion, endogenous glucose production increased quickly so that in toto the overall result was that there was no significant difference from that noted in the control group. The endogenous glucose production rate persisted, indicating that glucose did not independently diminish glucose production. In this neonatal lamb model, this would have occurred if glucose had a significant "adult-like" effect on neonatal glucose homeostasis.[12,13,15,16]

In summary, somatostatin and other known inhibitors of contra-insulin hormones have been infused in combination with glucose to determine the degree to which "isolated" glucose can influence glucose homeostasis. It is apparent from the data generated in this neonatal lamb model that the substrate does not tightly control glucose production in a manner parallel to that observed in the adult. These data contribute to the mounting body of evidence that a developmental maturation must occur throughout the neonatal period and beyond before "adult" control of glucose homeostasis is present.

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