0031-3998/86/2001-0049$02.00/0
PEDIATRIC RESEARCH

Vol. 20, No. 1, 1986
Printed in U.S.A.

Role of Glucose in the Regulation of Endogenous Glucose Production in the Human Newborn

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ABSTRACT. The role of plasma glucose concentration in the regulation of endogenous glucose production in the human newborn was examined by infusing glucose at 2.6–4.6 mg/kg·min as a continuous infusion to eight normal term appropriate for gestational age infants, five preterm, and six small for gestational age infants. All infants were healthy, had no overt clinical problems and were studied 6 h after their last feed. Glucose production rates were measured during the basal state and during glucose infusion by tracer dilution using [6,6$^2H_2$]glucose. The rate of glucose production during the basal state was similar in preterm and term appropriate for gestational age infants (appropriate for gestational age 3.53 ± 0.32, preterm 3.49 ± 0.38 mg/kg·min, mean ± SD), while it was higher in the small for gestational age infants (4.25 ± 0.98, $p < 0.03$) as compared with appropriate for gestational age. During glucose infusion, the peak glucose concentration was related to the rate of glucose infusion. The endogenous glucose production rates during glucose infusion were variable in the three groups. However, a negative correlation between peak glucose concentration and endogenous glucose production rate was observed ($r = -0.59$, $p = 0.006$). The insulin response to glucose infusion was comparable in all infants. In addition, three small gestational age and one preterm infants, who had become hypoglycemic in the immediate newborn period, were studied while they were receiving parenteral glucose and their plasma glucose had stabilized at 55.5 ± 10.25 mg/dl. Tracer kinetic studies showed persistence of endogenous glucose production in these infants even though they were receiving high rates of exogenous glucose infusion. These data show that, as in human adults, the endogenous glucose production in the newborn infant is regulated by plasma glucose and that prematurity and intrauterine growth retardation do not appear to have any significant effect on this regulation. However clinical hypoglycemia, probably as a result of counter-regulatory hormonal responses, can disturb this regulation. (*Pediatr Res* 20: 49–52, 1986)

Abbreviations

SGA, small for gestational age
AGA, appropriate for gestational age
PT-AGA, preterm AGA
Ra, systemic glucose production rate
Re, endogenous glucose production rate

One of the major events in the adaptation of the human neonate to extrauterine life is the abrupt shift in glucose metabolism at birth from a situation of net glucose uptake from the mother *in utero* to independent systemic glucose production. Disturbances in this adaptive response can lead to alterations in glucose homeostasis leading to hypoglycemia or to hyperglycemia in response to glucose infusion commonly observed in the low birth weight premature and the SGA infant. The exact mechanisms leading to such derangements are not fully understood. These questions can now be answered by measurements of glucose kinetics in such infants using safe stable isotopic tracer methods. Data in normal healthy newborn infants studied during the first few hours after birth show their rates of glucose production to range between 4 and 6 mg/kg·min (1, 2). While glucose kinetic studies have been done in infants of diabetic mothers (3, 4), similar measurements in the preterm and SGA infants have been limited (2, 5, 6). Cowett and colleagues (5, 6) utilized a recycling glucose tracer [U-^{13}C]glucose, and showed no difference in the rate of glucose turnover in preterm and term AGA infants.

The effects of exogenous glucose infusion on endogenous glucose turnover has been studied in adults and newborns in both humans and animals. While there is a complete suppression of endogenous glucose production in adults, the response in newborns has been variable (7–13). King *et al.* (4) observed 80% suppression of endogenous glucose production in term newborn infants. In contrast Cowett and coworkers (5, 6) in a study of slightly older infants observed a variable response—complete suppression in some and incomplete in others. The latter was seen more often in preterm infants. Similarly, failure to suppress endogenous glucose production in response to exogenous glucose infusion has been observed in newborn lambs and dogs (13–15). These differences in neonatal responses in comparison to those in adults have been attributed to immaturity of the neonatal glucose regulatory mechanisms (5). In the present study, we have measured the rates of glucose turnover in newborn term, preterm and SGA infants using nonrecycled [6,6-$^2H_2$]glucose tracer. In addition, the role of plasma glucose concentration in the regulation of endogenous glucose production rate was examined by quantifying the neonatal responses to exogenous glucose infused at rates comparable to endogenous glucose production rates.

MATERIALS AND METHODS

Glucose kinetics were measured during fasting (basal state) and in response to glucose infusion in eight term term AGA, eight SGA, and six PT-AGA infants. Their mean birth weight and gestational age are displayed on Table 1. One PT-AGA infant and one SGA infant were studied only during basal state. In addition, four infants, three SGA, and one PT-AGA, were studied while they were already receiving intravenous glucose for clinical hypoglycemia. AGA was defined as birth weight between 10th and 90th percentile for gestational age while SGA was defined as birth weight below the 10th percentile according to the Colorado intrauterine growth chart. The preterm AGA in-

Received April 29, 1985; accepted August 21, 1985.
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This work was supported by Grants HD 17336, HD 11089, M01-RR-00210 from the National Institute of Health. S.C.K. is the recipient of a Research Career Development Award. AM-00801, from the National Institute of Health.

Table 1. *Clinical profile of infants (mean ± SD)*

	Wt (g)	Gestational age (wk)
Term AGA (8)	3049 ± 338	39.1 ± 0.99
SGA (8)	2087 ± 439	38.0 ± 1.85
Preterm AGA (6)	2243 ± 208	35.5 ± 0.55

fants had birth weights in the same range as the SGA infants. The mean birth weight of perterm AGA and SGA infants were significantly less than term AGA infants ($p = 0.0002$, AGA *versus* PT-AGA; $p = 0.0002$, AGA *versus* SGA). All infants except two SGA infants were less than 24 h of age at the time of study and had fasted for 6 h. Dextrostix determinations of plasma glucose concentrations were done during the fasting period to insure that the infants did not become hypoglycemic. There was no history of birth asphyxia or other perinatal complications. All infants were clinically well, had stable blood glucose concentrations, did not require any respiratory assistance and were not receiving any medication, including antibiotics. All infants were born at Cleveland Metropolitan General Hospital and were studied in the Perinatal Clinical Research Center in a thermoneutral environment. The protocol was approved by the Institutional Committee on Investigation in Humans. Informed consent was obtained from the parents after fully explaining the procedures.

Two scalp vein needles were placed in peripheral veins in the extremities; one for intravenous infusion and the other for sampling of venous blood. Sampling site was kept patent by a slow infusion of isotonic saline solution. [6,6-$^2H_2$]glucose, 98 atom % excess, was obtained from Merck and Company, Inc. Dorvall, Quebec, Canada. A weighed amount was dissolved in sterile isotonic saline for intravenous infusion, sterilized by Millipore filtration (pore size 0.22 μ) and tested for sterility and pyrogenicity as described previously (12).

After obtaining a baseline blood sample, the tracer was administered as prime-constant-rate infusion at 60 μg/kg·min via a Holter pump. The ratio of prime to infusion rate was 90:1. The flow rates were checked after each study by quantitative determination. A steady state deuterium enrichment of plasma glucose was achieved within 60 min. During isotopic steady state, after 90 min of infusion, a glucose infusion as a 10% solution, at 2.6–4.6 mg/kg·min, was superimposed and was maintained for another 120 min. The rate of glucose infusion was chosen to approximate the endogenous glucose production rate. A new steady state isotopic enrichment was reached within 45–60 min. Heparinized blood samples were obtained at 15 to 30 min intervals throughout the study period. The number of samples obtained were adjusted according to the size of the baby. The samples were centrifuged immediately, plasma separated and stored at −10° C for later analysis.

Glucose concentration in the plasma and in the infusate was measured by the glucose oxidase method on a Beckman Glucose Analyser. The rate of [6,6-$^2H_2$]glucose infusion was calculated from the infusate glucose concentration and the rate of infusion. The deuterium enrichment of plasma glucose was measured by combined gas chromatography-mass spectrometry using the selected ion monitoring technique as described previously (12).

Glucose production rate was calculated from the dilution of the infused tracer in the plasma, by applying steady state kinetics. During exogenous glucose infusion, the endogenous glucose-production rate was estimated by subtracting the glucose infusion rate from the tracer determined glucose production rate.

RESULTS

Plasma glucose. The plasma glucose concentration during the basal period was significantly lower in the SGA and preterm AGA infants as compared with the normal term AGA infants (Fig. 1, Table 2).

In response to the exogenous glucose infusion, mean plasma glucose rose in all infants (Table 2). However, the rise in glucose was variable in the three groups. The mean peak glucose concentration was highest in AGA infants. The magnitude of rise in glucose was lowest in the SGA infants, in part reflecting a lower rate of exogenous glucose infusion. The peak glucose concentration observed in all infants was significantly related to the glucose infusion rate (Fig. 2). As the glucose infusion was continued, all infants showed a decrease in plasma glucose reflecting an appropriate adaptive response.

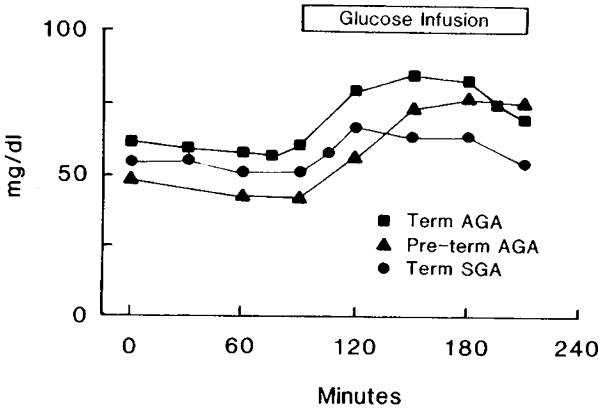

Fig. 1. The mean plasma glucose response to glucose infusion in the newborn infants. After a basal period of 90 min, glucose was infused intravenously at 2.6 to 4.6 mg/kg·min. See table 2 for respective SD for each datum point.

Plasma insulin. The mean levels of immunoreactive insulin during the basal state were similar in the three groups of infants. In response to glucose infusion, the plasma insulin levels increased in all infants. Even though the peak glucose concentrations were different in the three groups, the insulin responses were similar (Table 2).

Glucose kinetics. A steady state isotopic enrichment of plasma glucose was observed between 60–90 min in the basal state and after 60 min during glucose infusion. During fasting (basal state), the mean systemic Ra was 3.53 ± 0.32 mg/kg·min (mean ± SD) in the term AGA infants. Ra was significantly increased in the SGA infants 4.25 ± 0.98 (Table 3). In the preterm AGA, Ra (3.49 ± 0.38) was not significantly different from that observed in the AGA infants. During exogenous glucose infusion, the total Ra, quantified by tracer isotope dilution, was greater in preterm AGA than in AGA and SGA infants.

The Re, calculated by subtracting the exogenous glucose infusion rate from the total Ra, was variable reflecting different magnitudes of suppression of endogenous glucose production. The maximum suppression was seen in term AGA. The mean suppression of endogenous glucose production was 70% in AGA, 54% in SGA and 47% in preterm AGA infants. Re during glucose infusion was negatively correlated with the peak glucose concentration ($r = -0.59$, $p = 0.006$, Fig. 3) in the whole group. A significant correlation was also observed when the AGA group alone was examined. However, the correlation between peak glucose concentration and endogenous glucose production rate in the SGA and PT-AGA examined individually was not significant, possibly because of the small number of subjects in each group. There was no correlation between plasma insulin response and the endogenous glucose production rate.

Glucose kinetics in hypoglycemic infants. Four infants who had developed hypoglycemia in the immediate newborn period were studied after their blood glucose had stabilized for a period of 8–24 h. Their mean plasma glucose at the time of study was 55.5 ± 10.25 mg/dl and their mean plasma insulin level was 6.5 ± 2.06 μU/ml. They were receiving exogenous glucose infusion at 3.7, 3.1, 8.4, and 3.8 mg/kg·min. The total Ra, measured by tracer dilution, was 5.5, 5.4, 12.8, and 3.8 mg/kg·min while the rate of Re was 1.8, 2.4, 4.5, and 0.0 mg/kg·min. These data

Table 2. *Plasma glucose and insulin response to glucose infusion (mean ± SD)*

	Basal					Glucose infusion			
Min	0	30	60	75	90	120	150	180	210
Glucose (mg/dl)									
Term AGA	61.3 ± 10.1*	59.4 ± 13.6	58.1 ± 14.2	56.9 ± 13.0	61.6 ± 11.1	80.9 ± 13.4	85.8 ± 14.9	83.5 ± 15.0	71.3 ± 13.8
Preterm AGA	48.3 ± 10.3		41.3 ± 9.2		42.3 ± 7.1	57.8 ± 9.6	74.6 ± 12.3	78.2 ± 16.3	75.4 ± 14.3
Term SGA	53.7 ± 7.9	54.8 ± 13.7	50.4 ± 11.2		50.5 ± 11.7	67.4 ± 10.3	63.9 ± 12.8	64.0 ± 10.6	55.3 ± 13.3
Insulin (μU/ml)									
Term AGA	10.2 ± 5.1		9.9 ± 7.4		8.5 ± 6.4	9.4 ± 4.1	14.6 ± 6.2	22.6 ± 12.8	17.1 ± 6.4
Preterm AGA	7.6 ± 4.8		6.8 ± 2.2		6.0 ± 2.4	8.9 ± 6.6	14.3 ± 6.5		20.9 ± 15.1
SGA	5.2 ± 2.9		8.6 ± 3.9		6.0 ± 2.9	10.8 ± 4.4	15.5 ± 4.7	16.5 ± 4.8	12.7 ± 5.1

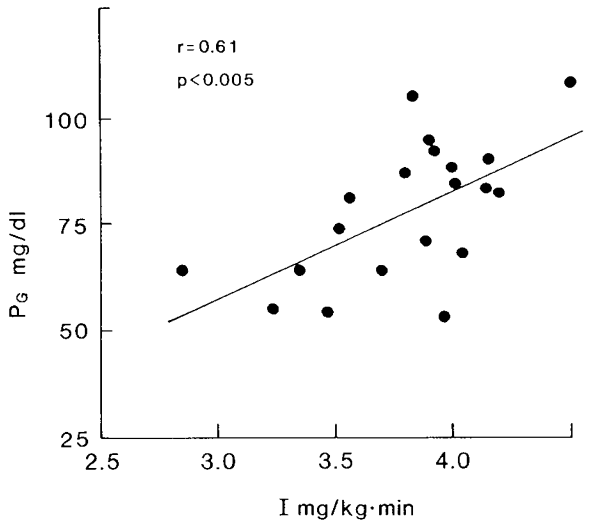

Fig. 2. The relation between peak (plateau) glucose concentration (P_G) and exogenous glucose infusion rate (I) is displayed: y = −17.7 + 2.52x; $r = 0.61$; $p < 0.005$.

indicate persistent endogenous glucose production during prolonged glucose infusion in three of these infants.

DISCUSSION

The regulation of hepatic glucose production has been examined in both the adult and the newborn in studies of humans, as well as animals (7–9, 16). During the basal state in normal adult humans and animals, the rate of glucose production is regulated by the interaction of insulin and glucagon. An unopposed action of insulin causes a decrease in glucose production while glucose production increases in the presence of unopposed glucagon effect (10, 17). During glucose infusion in normal adult humans and animals, suppression of endogenous glucose production occurs as a result of the autoregulatory effect of glucose and due to insulin action on the liver (7, 8). In the presence of a basal insulin concentration, infusion of exogenous glucose results in 70 to 90% inhibition of systemic glucose production (8, 9). However, when insulin concentration is increased, by high rates of glucose infusion, a complete suppression of glucose production occurs (11, 17). Thus, hepatic glucose production in adult animals and humans appears to be regulated by both glucose and insulin. Glucose alone appears to have its effect in suppressing glucose production, on an insulinized liver, via its effects on glycogen metabolism (18–21). Our present data in newborn infants are consistent with the observations in adults and show that regulation of hepatic glucose production is established in the human newborn and can be demonstrated within a few hours after birth. The finding of an inverse correlation between the peak (plateau) glucose concentration and the endogenous glucose production rate suggests that the glucose level achieved appears to be an important factor in determining the hepatic response and to explain the variation in the magnitude of suppression in different subjects. This may also be the explanation for the lesser degree of suppression in the infants of diabetic mother observed by us in a previous study (4) in which the infants of diabetic mothers did not achieve the same degree of hyperglycemia as the normal infants.

Our data are in contrast to the previously reported data in newborn animals where persistence of endogenous glucose production was observed by three different groups of investigators (13, 15, 22). Varma *et al.* (15) observed a continuous rise in glucose concentration in newborn dogs during constant infusion of glucose. In addition, the rate of hepatic glucose production diminished to a much lesser degree than in adult dogs. Their study contrasts with ours in that: a) The animals had been anesthetized with nembutal which may affect the metabolism of glucose. b) They used [2-^{3}H]glucose tracer where an excessive loss of label occurs due to futile cycling and thus will appear as continued glucose production. In our study, on the other hand, we used non-recycling tracer. c) Finally, the pups had been removed from their mothers only 3–5 h prior to the study; in contrast the adult dogs had fasted for 15–17 h. The newborn animals could, therefore, have been absorbing glucose from the gut. Sherwood *et al.* (22) in a study of the rhesus monkey neonate showed a marked reduction of endogenous glucose output in response to glucose. However, in a group of "sick" neonates (associated with 100% mortality), possibly as a result of counter-regulatory hormonal responses, marked hyperglycemia developed with no suppression of endogenous glucose output. Finally, in a study of newborn lambs, endogenous glucose production was shown to persist until very high rates of exogenous glucose infusion were used (13). However in that study, the animals consistently had high fasting plasma glucose concentration, suggesting a significant influence of counter-regulatory hormones. Thus difference in the animal data from that in the humans may be the result of varying degrees of stress, effects of anesthesia and/or species differences.

Previous data in human neonates have shown variable degrees of suppression of endogenous glucose production in response to exogenous glucose infusion (5). It has been suggested that this may be due to the immaturity of hepatic regulation or to relative insensitivity of the liver to insulin action. In the present study, all newborn infants mounted a significant insulin response and yet the hepatic response was variable, suggesting that insulin does not appear to be the dominant factor in regulation of hepatic glucose production. The inverse relationship between plateau glucose concentration and the Re supports the hypothesis that in the presence of insulin, plasma glucose concentration appears to be the important regulator of Re in the human neonate. This relation also suggests that at plasma glucose concentrations greater than 120 mg/dl, at least in term AGA infants, there will be complete suppression of hepatic glucose production and the liver in the newborn, as in adults, will actually start taking up glucose (18). No correlation between insulin levels and endogenous glucose production was observed in our study. The regula-

Table 3. *Plasma glucose, insulin, and glucose kinetics in the newborn infants (mean ± SD)*

	Basal			During glucose infusion				
	Glucose (mg/dl)	Insulin (μU/ml)	Ra (mg/kg·min)	Peak glucose (mg/dl)	Peak insulin (μU/ml)	Ra (mg/kg·min)	I* (mg/kg·min)	Re (mg/kg·min)
AGA	61.6 ± 11.11	8.5 ± 6.39	3.53 ± 0.32	90.1 ± 12.89	22.7 ± 12.67	5.19 ± 0.53	4.13 ± 0.22	1.07 ± 0.58
SGA	49.6 ± 10.91†	7.4 ± 4.29	4.25 ± 0.98†	64.6 ± 10.72‡	16.9 ± 5.08	5.33 ± 0.82	3.38 ± 0.47	1.83 ± 0.64
Preterm AGA	43.5 ± 6.35§	5.4 ± 2.09	3.49 ± 0.38	81.4 ± 12.18	19.3 ± 7.66	5.72 ± 0.50†	3.82 ± 0.26	1.89 ± 0.85

* Rate of infusion of exogenous glucose.
† $p \leq 0.05$ as compared with AGA.
‡ $p \leq 0.001$ as compared with AGA.
§ $p \leq 0.002$ as compared with AGA.

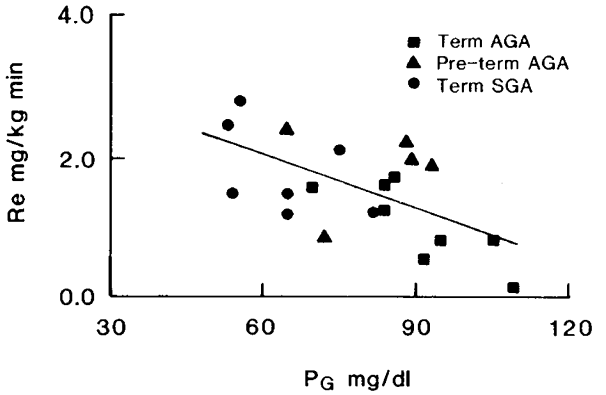

Fig. 3. The relation between peak (plateau) glucose concentration (P_G) and *Re* is displayed: y = 3.56 − 0.03x; $r = -0.59$; $p = 0.006$.

tory effect of glucose level upon hepatic release and uptake has been previously demonstrated in the isolated liver from the midterm human fetus (23). In that study, insulin in physiological concentration had no detectable effect on hepatic glucose output. The present data are consistent with these observations.

In contrast in the hypoglycemic infants, possibly as a result of counter-regulatory hormonal responses, there was continued Re. The small size of the infants did not permit the blood sampling required to measure levels of these hormones.

The data from the present study show that plasma glucose concentration has an important regulatory effect on hepatic glucose production in the human neonate. The responses to glucose levels are not affected by prematurity or intrauterine growth retardation. The mechanism of this regulation is most likely inactivation of glycogen synthetase in liver after the administration of glucose (20).

Finally SGA infants have a significantly higher rate of glucose production per kg in the basal state than AGA infants. This may be related to a larger mass of high glucose consuming tissue (brain) relative to total body mass.

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