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Alanine Administration Does Not Stimulate Gluconeogenesis in Preterm Infants

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Gluconeogenesis partially depends on sufficient precursor supply, and plasma alanine concentrations are generally low in preterm infants. Stimulation of gluconeogenesis may contribute to the prevention of hypoglycemia, an important clinical problem in these infants. In this study we evaluated the effect of extra precursor supply on gluconeogenesis in preterm infants. In 11 infants, gestational age ≤ 32 weeks, glucose production rate (GPR) and gluconeogenesis were measured using the [6,6-$^2H_2$]glucose dilution technique and mass isotopomer distribution analysis with [2-^{13}C]glycerol, respectively. Unlabeled glucose was administered throughout the study period at a rate of 22 μmol · kg^{-1} · min^{-1}. Five infants received alanine (1.5 mg · kg^{-1} · min^{-1}) during the last 3 hours of the study protocol, and 6 infants served as controls. In the control group the rate of gluconeogenesis and GPR remained constant at 4.0 ± 0.3 μmol · kg^{-1} · min^{-1} and 8.3 ± 0.6 μmol · kg^{-1} · min^{-1}, respectively. In the alanine group plasma alanine concentrations increased from 45 ± 23 to 829 ± 115 μmol/L (P = .001); gluconeogenesis and GPR did not differ from control: 3.8 ± 0.2 μmol · kg^{-1} · min^{-1} and 6.4 ± 2.0 μmol · kg^{-1} · min^{-1}, respectively. We conclude that administration of the gluconeogenic precursor alanine does not stimulate gluconeogenesis in preterm infants, despite a sharp increase in plasma alanine concentrations. We speculate either a restricted capacity of the enzymes involved in the gluconeogenic pathway or a low secretion rate of glucoregulatory hormones as causative mechanisms involved in the gluconeogenic pathway in the preterm neonate.

A LOW PLASMA GLUCOSE concentration is a frequently occurring disturbance in glucose metabolism in preterm infants, and may lead to serious short- and long-term complications.[1-3] The plasma glucose concentration is the result from a balance between glucose supply and glucose utilization. When glucose supply is insufficient to balance glucose utilization, hypoglycemia will follow.

Endogenous glucose production has been measured in many studies in both term and preterm infants under different circumstances.[4] Data on the contribution of gluconeogenesis to glucose production are scarce in preterm infants. In the 1970s it was suggested from measurements of plasma gluconeogenic precursor concentrations and liver enzyme activities that gluconeogenesis was limited in preterm infants.[5-9] Later, several stable isotope studies showed that preterm infants *are* capable of gluconeogenesis, even shortly after birth.[10-13] An important limitation of these studies is that gluconeogenesis was estimated. Until recently, reliable techniques for direct measurement of gluconeogenesis in vivo were not available.[14] Publications on gluconeogenesis in preterm infants applying these new techniques are therefore still scarce.[15]

Gluconeogenesis depends on sufficient precursor supply, adequate secretion rate of glucoregulatory hormones, and activity of the enzymes involved in glucose production and gluconeogenesis. In preterm infants plasma alanine concentrations are low compared to breastfed term infants or adults,[16-18] raising the question if gluconeogenesis can be stimulated by extra precursor supply.

The objective of the present study was to evaluate the effect of extra precursor supply on gluconeogenesis and endogenous glucose production in preterm infants by infusion of the main gluconeogenic precursor alanine.

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MATERIALS AND METHODS

Patients

Preterm infants were recruited from the Neonatal Intensive Care Unit at the Emma Children's Hospital AMC, Amsterdam. Preterm infants with a gestational age of 32 completed weeks or less were eligible for the study. We included only infants with a postnatal age between 1 and 8 days, because the incidence of low plasma glucose concentration is the highest in the first postnatal days. Exclusion criteria were hypoglycemia (for ethical considerations), birth weight less than 10th or greater than 90th percentile for gestational age,[19] sepsis, severe perinatal asphyxia (5-minute Apgar score < 7), congenital malformations, severe respiratory distress, need of vasopressor support, maternal diabetes, or glucose intolerance. Written informed consent by the parents was obtained in all cases. This study was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam.

Study Design

Eleven children were included in the study. Five infants received alanine intravenously (90 $mg \cdot kg^{-1} \cdot h^{-1}$) during the last 3 hours of the study. The control group (6 infants) received only glucose during the study. Assignment to the alanine or the control group was by random assignment. Infusions were administered through an intravenous (peripheral or central venous) catheter, previously introduced for clinical reasons. Blood samples were drawn from a second intravenous catheter in the opposite limb or, if present, from an intra-arterial line.

Enteral and parenteral nutrition were discontinued 6 hours before the study ($t = -12$ hours) and replaced by intravenous glucose supply (unlabeled) at a rate of 33 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (6 $mg \cdot kg^{-1} \cdot min^{-1}$). After obtaining a baseline blood sample at $t = -6$ hours (8 AM) for determination of background isotopic abundance and plasma glucose concentration, a primed (80 $\mu mol \cdot kg^{-1}$ body weight), continuous (0.9 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) infusion of [6,6-$^2H_2$]glucose (99% enriched, Isotec, Miamisburg, OH) was started to measure glucose production. [6,6-$^2H_2$]glucose, dissolved in sterile isotonic saline and sterilized by passage of the solution through a millipore filter (size 0.2 μm; Minisart, Sartorius, Göttingen, Germany), was administered by a calibrated syringe pump (Perfusor fm, Braun, Melsungen, Germany). Simultaneously, a primed (25 $mg \cdot kg^{-1}$ body weight), continuous (25 $mg \cdot kg^{-1} \cdot h^{-1}$) infusion of [2-^{13}C]glycerol (99% enriched, Isotec) was started to measure fractional gluconeogenesis using mass isotopomer distribution analysis (MIDA). [2-^{13}C]glycerol was chosen because glycerol enters the gluconeogenic pathway immediately before the triose-phosphate pool, the true precursor pool that must be enriched. Other gluconeogenic precursors like alanine may be lost in other metabolic pathways before they enter the triose-phosphate pool.[20] Two infants (one in each group) received only [6,6-$^2H_2$]glucose. Simultaneously with the start of the isotope infusions, the rate of exogenous glucose infusion (unlabeled) was diminished to 22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ (4 $mg \cdot kg^{-1} \cdot min^{-1}$) and maintained at this rate until the end of the study ($t = +3$ hours). Exogenous glucose was administered to maintain euglycemia. The rate of 22 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ was chosen because in our unit it is considered to be the lower limit of the required exogenous glucose supply in preterm infants.

After an equilibration period of 6 hours of stable isotope infusion, blood samples were collected every hour ($t = 0$ to $+3$ hours) for the measurement of isotopic enrichments and plasma glucose concentration. At $t = 0$ and $t = +3$ hours, blood was also collected for determination of alanine concentrations. Insulin concentrations were measured at $t = +3$ hours.

Assays

All measurements were performed in duplicate, except for the MIDA samples, and all samples of individual newborns were analyzed in the same run.

Gas chromatography/mass spectrometry (GC/MS) analyses were performed with a model 5890 Series II gas chromatograph coupled to a model 5989 A mass spectrometer (Hewlett Packard, Palo Alto, CA). We described the sample preparation for the MIDA technique using a combination of [2-^{13}C]glycerol and [6,6-$^2H_2$]glucose in detail previously.[14]

Plasma glucose concentration was measured by the glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Mijdrecht, The Netherlands). Alanine concentrations were measured with an enzymic micromethod.[21] Insulin concentrations were measured using a radioimmunoassay (Pharmacia Diagnostics, Uppsala, Sweden).

Calculations and Statistics

The rate of appearance (Ra) of plasma glucose was calculated by the isotope dilution technique from the [6,6-$^2H_2$] enrichment of glucose, using calculations for steady-state kinetics, adapted for the use of stable isotopes[22]: $Ra = (E_i/E_p) \times I$, where E_i and E_p are the [6,6-$^2H_2$] enrichments of infusate and plasma, respectively, and I is the infusion rate of [6,6-$^2H_2$]glucose. To determine endogenous glucose production rate (GPR), exogenously infused glucose was subtracted from glucose Ra.

Precursor pool enrichment (p) (interassay variation, 9%) and fractional gluconeogenesis (f) (interassay variation, 6.8%) were calculated from the mass isotopomer distribution pattern of unlabeled, singly and doubly labeled glucose derived from [2-^{13}C]glycerol as previously described.[14,20,23] The absolute rate of gluconeogenesis is calculated as the product of f $\times$ glucose Ra.

To investigate the difference in glucose kinetics between the alanine and control group, measurements from $t = 1$ hour onward were compared with analysis of repeated measurements, using the data at $t = 0$ hours as a covariate (proc mixed of SAS 6.12, SAS Institute, Cary, NC). Paired data were analyzed by the paired *t* test. Data are reported as mean $\pm$ SEM, unless otherwise stated. Statistical significance was set at $P < .05$.

RESULTS

Clinical Data

Mean gestational age was 28 6/7 $\pm$ 2.0 (SD) weeks in the alanine group and 30 0/7 $\pm$ 1.8 weeks in the control group (difference not significant [NS]). Mean birth weight was 1,359 $\pm$ 459 and 1,315 $\pm$ 244 grams, respectively (NS). All infants were appropriate for gestational age. Postnatal age was not significantly different: 5.0 $\pm$ 1.4 days in the alanine group and 4.5 $\pm$ 1.8 days in the control group. The infants were clinically stable, had normal body temperature, normal acid base status, and normal oxygen saturation and carbon dioxide concentrations. Two infants in the control group were ventilated with mild ventilatory settings and received morphine for sedation, consistent with the routines in our nursery. Most infants received antibiotics, but none had positive blood cultures or clinical signs of infection. In both groups 4 mothers were treated with antenatal steroids. All infants in the alanine group were treated with caffeine for apnea of prematurity, compared to 3 of the 4 spontaneously breathing infants in the control group. Parameters of glucose kinetics were not different between infants with and without morphine or caffeine therapy. In addition, there were no differences between infants born to

Table 1. Isotopic Enrichments and Plasma Glucose Concentrations During the Study

	Time (h)			
	0	1	2	3
[6,6-$^2H_2$]glucose				
Alanine	2.96 ± 0.16	2.98 ± 0.21	3.10 ± 0.14	3.15 ± 0.23
Control	3.00 ± 0.10	2.91 ± 0.10	2.98 ± 0.10	2.87 ± 0.05
[$^{13}C_1$]glucose				
Alanine	3.61 ± 0.26	3.77 ± 0.16	3.76 ± 0.22	3.79 ± 0.22
Control	3.40 ± 0.11	3.48 ± 0.19	3.52 ± 0.15	3.54 ± 0.17
[$^{13}C_2$]glucose				
Alanine	1.31 ± 0.16	1.30 ± 0.05	1.30 ± 0.07	1.26 ± 0.03
Control	1.25 ± 0.07	1.30 ± 0.06	1.27 ± 0.05	1.31 ± 0.03
Plasma glucose concentration				
Alanine	3.7 ± 0.2	3.8 ± 0.2	3.5 ± 0.1	3.4 ± 0.2
Control	4.0 ± 0.4	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.2

NOTE. Data are means ± SEM.

mothers treated with antenatal steroids and those born to untreated mothers.

Glucose Kinetics

Both plasma glucose concentrations and isotopic enrichments were stable during the study period and approximate steady-state (defined by a coefficient of variation of <10%) was reached from t = 0 to t = +3 hours (Table 1).

Plasma alanine concentrations increased during alanine infusion from 45 ± 23 to 829 ± 115 μmol/L (P = .001), but remained constant in the control group (53 ± 12 *v* 55 ± 13 μmol/L, NS) (Fig 1). During alanine infusion, GPR and gluconeogenesis did not increase (Figs 2 and 3): GPR was 7.9 ± 1.4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ at t = 0 hours and 6.4 ± 2.0 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ at t = +3 hours (NS), and gluconeogenesis was 4.0 ± 0.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ at t = 0 hours and 3.8 ± 0.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ at t = +3 hours (NS). In the control group glucose production and gluconeogenesis remained constant during the last 3 hours at 7.7 ± 0.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and 3.9 ± 0.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, respectively. From t = 0 hours until t = +3 hours, the plasma glucose concentration remained constant in the control group (Fig 4): 4.0 ± 0.4 at t = 0 and 4.2 ± 0.2 mmol/L at t = +3 hours. In the alanine group, the plasma glucose concentration showed a small albeit statistically significant decrease (from 3.7 ± 0.2 at t = 0 to 3.4 ± 0.2 mmol/L at t = +3 hours; P = .005). Insulin concentrations at t = +3 hours were not different between the groups: median 30 pmol/L (range, 25 to 80) in the alanine group and median 30 pmol/L (range, 20 to 85) in the control group.

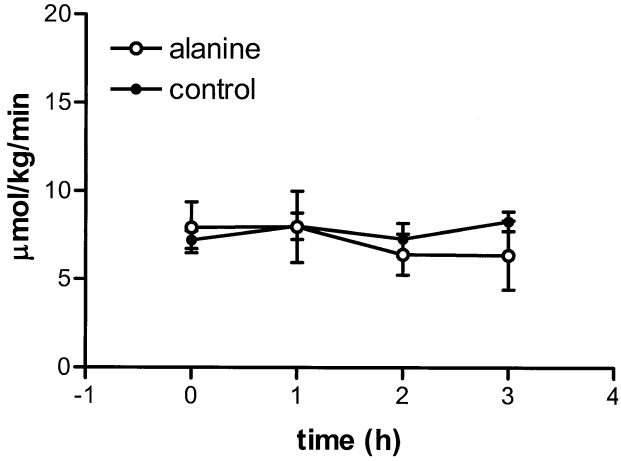

Fig 2. Endogenous glucose production rate. Data are means ± SEM.

DISCUSSION

In preterm infants, low plasma glucose concentrations are frequent. The low plasma amino acid concentrations in preterm infants suggest that extra precursor supply could be beneficial for stimulation of gluconeogenesis and therefore glucose production in these infants.[16-18] The present study was designed to evaluate this possibility. Our study shows that, despite the low plasma alanine concentrations *before* and the increase in

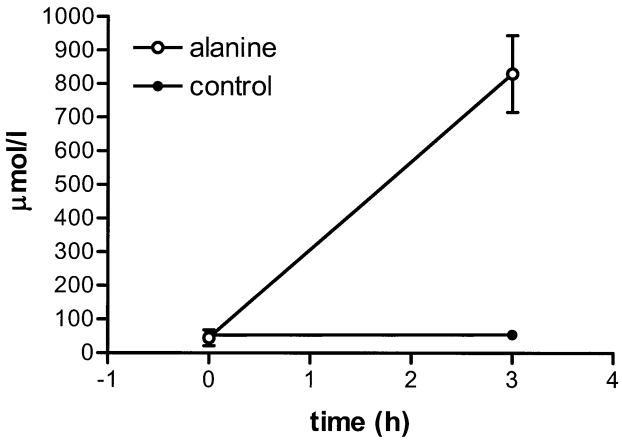

Fig 1. Plasma alanine concentrations. Data are means ± SEM. In the alanine group there was a significant increase from t = 0 to t = 3 hours (P = .001).

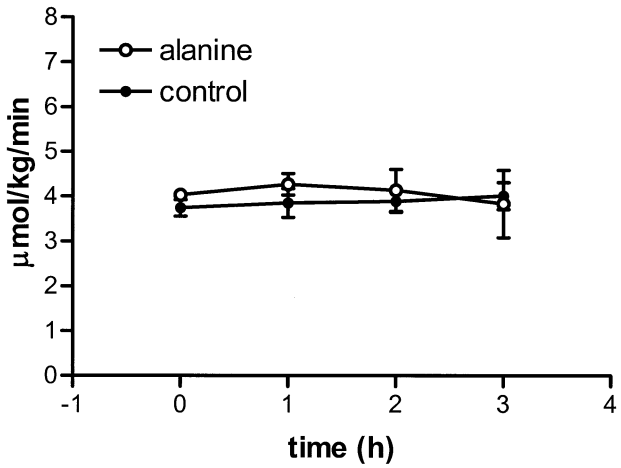

Fig 3. Rate of gluconeogenesis. Data are means ± SEM.

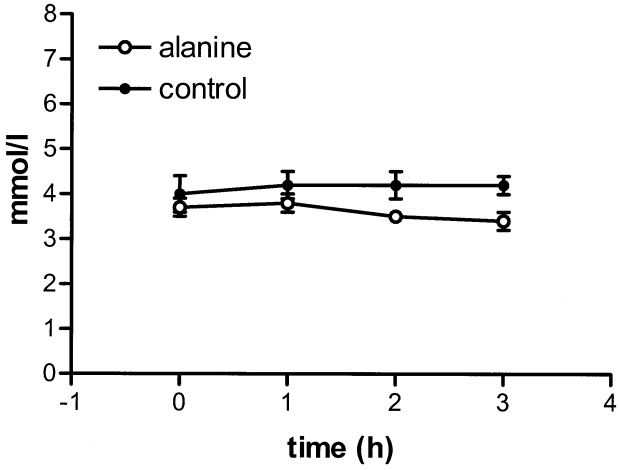

Fig 4. Plasma glucose concentrations. Data are means ± SEM. In the alanine group the plasma glucose concentration decreased slightly (*P* = .005).

plasma concentration *during 3* hours of alanine administration, the extra precursor supply did not result in an increase in gluconeogenesis.

There are no studies measuring glucose production in response to alanine infusion in preterm infants or healthy children. In prolonged fasted adults, alanine infusion is able to stimulate glucose production when plasma alanine concentrations and GPR are low.[24-26] In healthy children, plasma glucose and alanine concentrations are lower than in adults, both after an overnight and after a 30-hour fast.[18] In malnourished children and in children with malaria fasted overnight, plasma alanine concentrations are even lower than in healthy children. In both groups alanine infusion has been shown to stimulate glucose production, with a concomitant increase in plasma glucose concentration.[27,28] These data indicate that gluconeogenic precursor supply influences gluconeogenesis in overnight fasted children when plasma precursor concentrations are low. According to the data from a previous study of our group, this condition is also fulfilled in preterm infants, and therefore a positive effect of precursor supply on gluconeogenesis was expected.[29]

A difference between our study and the studies in older children is the administration of unlabeled glucose, necessary to prevent hypoglycemia in our preterm infants, whereas the older children were fasted overnight. The glucose infused during the study could have influenced our results when it would largely suppress glucose production. We therefore chose a glucose infusion rate (22 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) in the lower range of the commonly prescribed glucose intake in preterm infants (22 to 55 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}). This infusion rate did not suppress endogenous production as the latter still accounted for approximately 25% of glucose appearance in our infants. When glucose appearance is sufficient to account for glucose demands, this could explain the absence of an effect of alanine supply on endogenous glucose production. However, the extra alanine supply could still have stimulated gluconeogenesis, while endogenous production remained unchanged due to a concomitant decline in glycogenolysis, a phenomenon seen in adults.[30] This did not occur in our study. Besides, the chosen study design does not preclude stimulation of gluconeogenesis. In a comparable study design, our group showed that administration of intravenous lipids stimulates gluconeogenesis significantly.[31]

Although we cannot completely exclude the impact of the nutrients administered prior to the study, we think this played a limited role. There were no differences between the groups in the amount of macronutrients they received. In addition, the plasma alanine concentrations before alanine administration were very low, much lower than in the malnourished infants or children with malaria.[27,28]

The lack of stimulation we found in the present study cannot be explained by insufficient supply of alanine. If the administered alanine would have been completely converted into glucose, gluconeogenesis would have increased with approximately 8.5 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}.

We therefore speculate that, in the preterm infants we studied, the lack of stimulation of gluconeogenesis was not due to insufficient precursor supply. Other explanations for the lack of stimulation of gluconeogenesis by precursor supply could be: (1) low activity of enzymes involved in gluconeogenesis. This possibility is supported by the low glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activities found in postmortem studies in preterm infants compared to term infants.[4,8,32] However, an obvious limitation of these studies is that differences may be related to the clinical course and cause of death, rather than factors like gestational age. Although at least 50% of GPR was derived from gluconeogenesis in our infants, this does not preclude the possibility of limitations in the gluconeogenic enzymes, since the absolute amount of gluconeogenesis ($\sim$4 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) was low in the infants we studied. (2) Disturbances in the hormonal regulation of glucose metabolism resulting in impaired gluconeogenesis could be lack of stimulation by low glucagon, or inhibition of gluconeogenesis by high insulin concentrations. Glucagon stimulates both glycogenolysis and gluconeogenesis. Due to limitations in the amount of blood, we were not able to measure glucagon concentrations in the present study. Previously an increase in plasma glucagon concentration was shown after intravenous alanine administration in preterm infants.[33] It is therefore not likely that low glucagon concentrations are the explanation for the absence of an increase in gluconeogenesis in this study. Insulin concentrations were low and comparable between the alanine and control group at the end of the study, precluding the possibility of inhibition of glucose production by hyperinsulinemia. We therefore speculate that, in the preterm infants we studied while receiving exogenous glucose, the lack of stimulation of gluconeogenesis is not due to insufficient precursor supply, suppression of endogenous glucose production, or hormonal factors. Limited activity of the enzymes involved in the gluconeogenic pathway is a more likely causative mechanism.

The decline in plasma glucose concentration during alanine infusion was unexpected but has been reported previously.[33] The drop in glucose concentration in our study cannot be ascribed to a decrease in glucose production as this was stable in our study. Another explanation could be an increased glu-

cose clearance. Alanine is a well-known insulin secretagogue,[34-36] but stimulation of insulin secretion is an unlikely explanation in our infants since plasma insulin concentrations were low and comparable in both groups. This observation is therefore unexplained.

In summary, administration of the gluconeogenic precursor alanine does not result in an increase in plasma glucose concentration, endogenous GPR, or gluconeogenesis. We speculate a restricted capacity of the enzymes involved in the gluconeogenic pathway in the preterm neonate, although a low secretion rate of hormones necessary for stimulation of gluconeogenesis cannot be excluded completely.

REFERENCES

1. Lubchenco LO, Bard H: Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. Pediatrics 47: 831-838, 1971
2. De Leeuw R, de Vries IJ: Hypoglycemia in small-for-dates newborn infants. Pediatrics 58:18-22, 1976
3. Cornblath M, Schwartz R: Disorders of Carbohydrate Metabolism in Infancy (ed 3). Boston, MA, Blackwell Scientific, 1991
4. Cowett RM: Principles of Perinatal-Neonatal Metabolism (ed 2). New York, NY, Springer Verlag, 1998
5. Haymond MW, Karl IE, Pagliara AS: Increased gluconeogenic substrates in the small-for-gestational-age infant. N Engl J Med 291: 322-328, 1974
6. Mestyán J, Soltész G, Schultz K, et al: Hyperaminoacidemia due to the accumulation of gluconeogenic amino acid precursors in hypoglycemic small-for-gestational age infants. J Pediatr 87:409-414, 1975
7. Williams PR, Fiser RH Jr, Sperling MA, et al: Effects of oral alanine feeding on blood glucose, plasma glucagon and insulin concentrations in small-for-gestational-age infants. N Engl J Med 292:612-614, 1975
8. Marsac C, Saudubray JM, Moncion A, et al: Development of gluconeogenic enzymes in the liver of human newborns. Biol Neonate 28:317-325, 1976
9. Stanley CA, Anday EK, Baker L, et al: Metabolic fuel and hormone responses to fasting in newborn infants. Pediatrics 64:613-619, 1979
10. Cowett RM, Wolfe RR: Glucose and lactate kinetics in the neonate. J Dev Physiol 16:341-347, 1991
11. Bougnères P-F, Karl IE, Hillman LS, et al: Lipid transport in the human newborn: Palmitate and glycerol turnover and the contribution of glycerol to neonatal hepatic glucose output. J Clin Invest 70:262-270, 1982
12. Fjeld CR, Cole FS, Bier DM: Energy expenditure, lipolysis, and glucose production in preterm infants treated with theophylline. Pediatr Res 32:693-698, 1992
13. Sunehag A, Gustafsson J, Ewald U: Extremely preterm infants (<28 weeks) are capable of gluconeogenesis from glycerol on the first day of life. Pediatr Res 36:550-557, 1996
14. Ackermans MT, Pereira Arias AM, Bisschop PH, et al: The quantification of gluconeogenesis in healthy men by $^{2}H_2O$ and [2-^{13}C] glycerol yields different results: Rates of gluconeogenesis in healthy men measured with $^{2}H_2O$ are higher than those measured with [2-^{13}C] glycerol. J Clin Endocrinol Metab 86:2220-2226, 2001
15. Sunehag A, Haymond MW, Schanler RJ, et al: Gluconeogenesis in very low birth weight infants receiving total parenteral nutrition. Diabetes 48:791-800, 1999
16. Wu PYK, Edwards N, Storm MC: Plasma amino acid pattern in normal breastfed infants. J Pediatr 109:347-349, 1986
17. van Goudoever JB, Colen T, Wattimena JLD, et al: Immediate commencement of amino acid supplementation in preterm infants: Effect on serum amino acid concentrations and protein kinetics on the first day of life. J Pediatr 127:458-465, 1995
18. Haymond MW, Karl IE, Clarke WL, et al: Differences in circulating gluconeogenic substrates during short-term fasting in men, women and children. Metabolism 31:33-42, 1982
19. Kloosterman GJ: On intrauterine growth. Int J Gynaecol Obstet 8:895-912, 1970
20. Neese RA, Schwartz J-M, Faix D, et al: Gluconeogenesis and intrahepatic triose phosphate flux in response to fasting or substrate loads. J Biol Chem 270:14452-14466, 1995
21. Schutgens RBH, Tjoe Awie C, Beemer FA, et al: Rapid enzymic micromethod for the quantitative determination of L(+)alanine in blood and urine. Clin Chim Acta 80:1-5, 1977
22. Wolfe RR: Calculations of substrate kinetics: Single pool model, in Wolfe RR (ed): Radioactive and Stable Isotope Tracers in Biomedicine. Principles and Practice of Kinetic Analysis. New York, NY, Wiley-Liss, 1992, pp 119-144
23. Hellerstein MK, Neese RA: Mass isotopomer distribution analysis: A technique for measuring biosynthesis and turnover of polymers. Am J Physiol 263:E988-E1001, 1992
24. Cahill GF Jr: Starvation in man. N Engl J Med 282:668-675, 1970
25. Felig P, Marliss E, Owen OE, et al: Role of substrate in the regulation of hepatic gluconeogenesis in fasting man. Adv Enzyme Regul 7:41-46, 1969
26. Felig P, Marliss E, Pozefsky T, et al: Amino acid metabolism in the regulation of gluconeogenesis in man. Am J Clin Nutr 23:986-992, 1970
27. Dekker E, Hellerstein MK, Romijn JA, et al: Glucose homeostasis in children with falciparum malaria: Precursor supply limits gluconeogenesis and glucose production. J Clin Endocrinol Metab 82: 2514-2521, 1977
28. Kerr DS, Stevens MCG, Picou DIM: Fasting metabolism in infants: II. The effect of severe undernutrition and infusion of alanine on glucose production estimated with U-^{13}C-glucose. Metabolism 27: 831-848, 1978
29. van Kempen AAMW, Romijn JA, Ruiter AFC, et al: Adaptation of glucose production and gluconeogenesis to diminishing glucose infusion in preterm infants at varying gestational ages. Pediatr Res 53:628-634, 2003
30. Roden M, Stingl H, Chandramouli V, et al: Effects of free fatty acid elevation on postabsorptive endogenous glucose production and gluconeogenesis in humans. Diabetes 49:701-707, 2000
31. van Kempen AAMW, Romijn JA, Ackermans MT, et al: Intravenous fat emulsion stimulates gluconeogenesis in preterm infants. Clin Nutr 20:25, 2001 (suppl 3, abstr)
32. Hume R, Burchell A: Abnormal expression of glucose-6-phosphatase in preterm infants. Arch Dis Child 68:202-204, 1993
33. Sann L, Ruitton A, Mathieu M, et al: Effect of intravenous L-alanine on plasma glucose, insulin and glucagon, blood pyruvate, lactate and beta-hydroxybutyrate concentrations in newborn infants: Study in term and preterm newborn infants. Acta Paediatr Scand 67:297-302, 1978
34. Floyd JC Jr, Fajans SS, Pek S, et al: Synergistic effect of certain amino acid pairs upon insulin secretion in man. Diabetes 19:102-108, 1979
35. Floyd JC Jr, Fajans SS, Pek S, et al: Synergistic effect of essential amino acids and glucose upon insulin secretion in man. Diabetes 19:109-115, 1979
36. Grasso S, Messina A, Distefano G, et al: Insulin secretion in the premature infant: Response to glucose and amino acids. Diabetes 22:349-353, 1973