# 153 Pathophysiology of Neonatal Hypoglycemia

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## INTRODUCTION

Hypoglycemia in neonates has been a topic of major concern and controversy for many decades. This arises from two competing clinical issues. On the one hand, there is the serious risk for seizures and permanent brain injury for a small number of infants born with persistent forms of hypoglycemia if it is not detected early and treated adequately. For example, more than half of children with genetic forms of congenital hyperinsulinism have seizures and permanent brain injury[1-3] that might have been prevented or ameliorated if their hypoglycemia had been diagnosed and treated before their discharge from the newborn nursery. On the other hand, there is a competing need to avoid overdiagnosis and unnecessary interventions, because hypoglycemia to various degrees is very common in normal infants during the first 1 to 2 days of life and usually has no apparent consequence. For example, in normal newborns, mean plasma glucose concentrations transiently drop by 25 to 30 mg/dL from the fetal range of 70 to 90 mg/dL[4] to a nadir of approximately 55 to 60 mg/dL immediately after birth[5,6]; glucose levels then quickly rise within 1 to 2 days back into the normal range of 70 to 100 mg/dL for infants, children, and adults. This phenomenon of transitional neonatal hypoglycemia in the normal newborn

can obviously create difficulty and confusion in recognizing cases with disorders of permanent or persistent hypoglycemia for the first day or first days after birth. Contributing to the difficulty in balancing the concerns about persistent, potentially damaging, rare forms of hypoglycemia and the commonness of transitional hypoglycemia in normal newborns is the imbalance in our understanding of these conditions. The persistent forms of hypoglycemia that can present in the newborn have been well described and their diagnosis and treatment have been well defined. However, the mechanism(s) and management of transitional neonatal hypoglycemia remain poorly understood, further complicating efforts to distinguish the reason for hypoglycemia in individual cases. The purposes of this chapter are (1) to review the pathophysiology of neonatal hypoglycemia with an emphasis on the mechanism(s) underlying transitional neonatal hypoglycemia in normal newborns, (2) to describe the prolonged hyperinsulinism disorder that commonly occurs in neonates with perinatal stress such as birth asphyxia or intrauterine growth retardation, and (3) to outline briefly the diagnosis and management of the major genetic or other persistent hypoglycemia disorders that are most likely to be encountered in the neonatal period.

## ESSENTIAL ELEMENTS OF NORMAL GLUCOSE HOMEOSTASIS

### DEFINITION OF HYPOGLYCEMIA

Clinical hypoglycemia is a plasma glucose concentration low enough to cause signs or symptoms of impaired brain function. Clinical recognition of hypoglycemia is most reliably made by Whipple's triad (symptoms compatible with hypoglycemia associated with a low plasma glucose concentration and relief of symptoms when glucose concentration is restored to normal). Recognition may be difficult when the patient cannot communicate symptoms (e.g., infants and neonates). The physiologically normal range of plasma glucose concentration (70 to 100 mg/dL, 3.9 to 5.6 mmol/L) appears to be the same across all ages from the fetus to adulthood. However, it must be stressed that hypoglycemia cannot be defined as a specific plasma glucose value, because (1) the responses to hypoglycemia occur across a range of plasma glucose concentrations[7] and (2) brain responses may be altered by availability of alternative fuels (ketones). In addition, there are many potential artifacts in the measurement plasma glucose concentration: (1) specimens of venous or capillary blood may have lower glucose concentrations than the arterial plasma to which the brain is exposed,[8] (2) the glucose concentration in plasma is approximately 15% higher than that in whole blood, (3) glucose concentrations in blood decline rapidly with delays in processing,[9] and (4) glucose concentration measurements by bedside testing have a 15% imprecision and can be affected by multiple artifacts of sampling and operator errors.

### BRAIN INJURY DUE TO HYPOGLYCEMIA

Glucose is the major fuel for brain metabolism. The brain has a very high rate of metabolism and depends on a constant supply of glucose. Because the brain has little or no stores of glycogen, interruption of glucose delivery can have devastating consequences, including seizures and permanent brain injury.[1-3] Recovery from brief periods of hypoglycemia is usually complete, but permanent brain injury can occur depending on the severity and the duration of the hypoglycemia. A specific plasma glucose concentration that causes brain damage cannot be assigned, because of the reasons noted earlier that make it not possible to assign a specific glucose value for defining hypoglycemia and because other factors (e.g., duration of hypoglycemia) can affect the extent of injury.

### SYMPTOMS OF HYPOGLYCEMIA

The symptoms of hypoglycemia reflect brain responses to glucose deprivation. These are not specific to hypoglycemia and fall into two categories *Neurogenic symptoms* reflect the activation of sympathetic nervous system discharge triggered by hypoglycemia. These symptoms are both adrenergic (tachycardia, palpitations, tremor, anxiety) and cholinergic (sweating, hunger, paresthesias). Awareness of hypoglycemia depends on perception of these neurogenic responses. *Neuroglycopenic symptoms* are caused by brain dysfunction due to deficient glucose supply. The glucose threshold for neurogenic responses to hypoglycemia can be decreased by previous episodes of hypoglycemia for 24 hours or more (hypoglycemia unawareness or hypoglycemia-associated autonomic failure)[10] but the glucose threshold for neuroglycopenia is not affected by prior exposure to hypoglycemia.

### GLUCOSE THRESHOLDS FOR RESPONSE TO HYPOGLYCEMIA

Because of the critical importance of glucose for brain function, maintenance of normal plasma glucose concentrations is highly protected. As shown in Figure 153-1, on the basis of studies of acute insulin-induced hypoglycemia, the first stage of defense is suppression of insulin secretion by pancreatic islets as plasma glucose concentrations fall below 80 mg/dL.[11-15] The second stage of defense is secretion of counterregulatory hormones to stimulate glucose release from liver glycogen stores when plasma

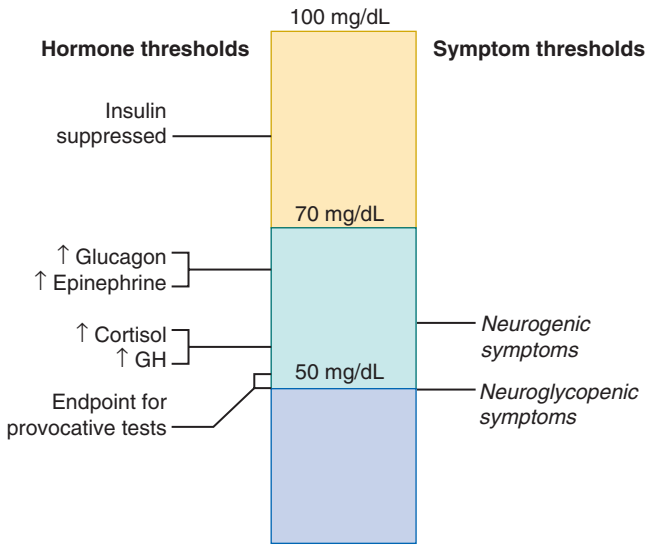


**Figure 153-1 Glucose thresholds for neuroendocrine and neuroglycopenic responses to hypoglycemia.** This demonstrates the progressive physiologic responses to falling plasma glucose concentrations and the thresholds for symptoms of hypoglycemia. The threshold used for ending provocative fasting studies and for performing laboratory evaluation of the fasting fuel response to hypoglycemia is 50 mg/dL, demonstrated by the *dashed line. GH,* Growth hormone. (Modified from Schwartz NS, Clutter WE, Shah SD, et al: Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest* 79(3):777–781, 1987; Heller SR, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40(2): 223–226, 1991; and Cryer PE, Gerich JE: Glucose counterregulation, hypoglycemia, and intensive insulin therapy in diabetes mellitus. *N Engl J Med* 313(4):232–241, 1985.)

glucose concentrations fall to approximately 65 mg/dL (glucagon release from pancreatic islets and sympathetic discharge as reflected by a rise in plasma epinephrine concentration). Plasma cortisol and growth hormone concentrations also rise as glucose concentration falls to approximately 60 mg/dL.[16,17] Although increases in the concentrations of these hormones do not affect glucose levels in the short term, they are required for long-term glucose homeostasis. The third stage of response to hypoglycemia is impairment of brain function itself at a glucose threshold of approximately 50 mg/dL. The glucose thresholds shown in Figure 153-1 come primarily from studies in adults but they have been shown to also apply to children.[17,18] In addition, observations of responses to hypoglycemia in infants and children with various hypoglycemia disorders suggest that glucose thresholds are essentially the same across all ages.[19,20]

## METABOLIC RESPONSES TO HYPOGLYCEMIA

In addition to the hormone responses to hypoglycemia noted already, there is a well-coordinated system of metabolic responses, which serves to maintain delivery of fuel to the brain and other tissues during fasting once glucose supplies from a meal become exhausted. These responses include (1) hepatic glycogenolysis to release glucose stored in liver glycogen for use by the brain; (2) supplementation of hepatic production of glucose by gluconeogenesis using substrates such as lactate, pyruvate, and amino acids derived from muscle and other peripheral tissues; (3) during prolonged fasting, increase in adipose tissue lipolysis to provide free fatty acids as a fuel for peripheral tissues, and to spare glucose for oxidation by the brain (lipolysis also releases glycerol, which becomes a major substrate for gluconeogenesis); and (4) oxidation of circulating free fatty acids by hepatic ketogenesis to form ketones (β-hydroxybutyrate and acetoacetate) as substrates derived from adipose tissue fat stores that can be used as fuel by the brain.

## DIAGNOSIS OF HYPOGLYCEMIA BASED ON METABOLIC FUEL RESPONSES

The integrity of the various metabolic and endocrine systems required for glucose homeostasis can be most readily tested by examination of the changes in plasma levels of the major fuels at the end of a fasting test when plasma glucose concentrations fall towards 50 mg/dL (Figure 153-2, *A*).[21-24] As shown in Figure 153-2, *B,* measurement of the concentrations of lactate (a major gluconeogenic substrate), β-hydroxybutyrate (the major ketone), and free fatty acids (released by lipolysis) provides a robust basis for the differential diagnosis of hypoglycemia disorders. Note that because plasma insulin concentrations are commonly insufficiently elevated for one to diagnose hyperinsulinism, the diagnosis is most reliably made on the basis of suppressed levels of β-hydroxybutyrate and free fatty acids. Confirmation of hyperinsulinism can be easily done by the demonstration of an inappropriately large glycemic response to glucagon[25] (reflecting inappropriate conservation of liver glycogen reserves). Similarly, plasma cortisol and growth hormone levels are often not high enough to rule out pituitary deficiency, and specific diagnostic tests are frequently necessary.[26] In the subsequent sections of this chapter on transitional neonatal hypoglycemia in normal newborns and persistent hypoglycemia in high-risk neonates, we will analyze the mechanism(s) responsible for hypoglycemia using the fasting systems approach outlined in Figure 153-2, *B.*

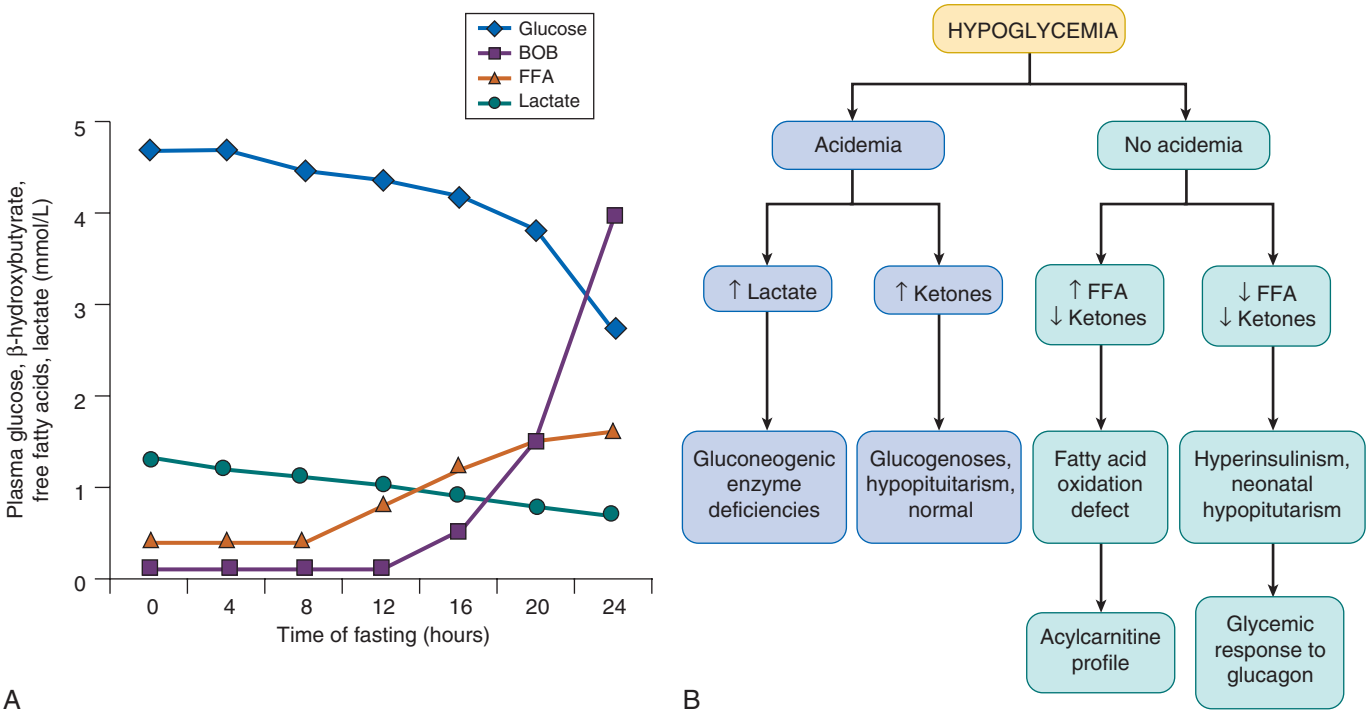


**Figure 153-2** **A,** The metabolic fuel response to fasting.[21-24] Note that plasma glucose concentration falls as liver glycogen stores become depleted. There is a small decrease in lactate concentration, demonstrating reducing gluconeogenesis. Ketone production increases to provide an alternative fuel for the brain as plasma glucose concentration is falling towards hypoglycemic levels. **B,** Interpreting the cause of hypoglycemia on the basis of the interpretation of the "critical sample." Note that hypoketotic hypoglycemia in hypopituitarism is seen only in neonatal hypopituitarism, and the older child with hypopituitarism generally has ketotic hypoglycemia. Confirmatory testing for hyperinsulinism includes a glycemic response to glucagon, although neonatal hypopituitarism can sometimes also have a positive response (possibly related to perinatal stress hyperinsulinism; see the text). Acylcarnitine profile is a confirmatory test for suspected fatty acid oxidation defects. Examples of gluconeogenic enzyme deficiencies include glucose 6-phosphatase, fructose 1,6-bisphosphatase, and pyruvate carboxylase deficiencies. *BOB,* β-Hydroxybutyrate; *FFA,* free fatty acids.

## FETAL GLUCOSE REGULATION

Before birth, fetal metabolism is supported almost entirely by oxidation of glucose. This glucose is derived from the maternal plasma, where its concentration is regulated by maternal insulin secretion. This constant supply of glucose means that fasting metabolic systems (glycogenolysis, gluconeogenesis, and fatty acid oxidation) are not activated in the fetus.

Fetal insulin secretion is responsive to changes in fetal glucose concentrations but the concentrations of fetal plasma glucose are primarily controlled by the plasma glucose concentrations in the mother. Thus the function of fetal insulin secretion is primarily to regulate growth rather than glucose levels in the fetus. For example, mothers with inactivating mutations of glucokinase (maturity-onset diabetes of the young type 2) have mild persistent hyperglycemia, which leads to increased insulin secretion in their unaffected fetus and birth weight increased by approximately 0.25 kg.[27] Conversely, fetuses with glucokinase-inactivating mutations who have an unaffected mother have reduced insulin secretion, resulting in approximately 0.4 kg lower birth weight. Early in gestation, the fetal brain is perfused with fetal plasma glucose concentrations that are equal to maternal levels. Fetal glucose levels near term fall slightly below maternal values, reflecting the high rate of glucose consumption by the fetus.[4] However, at birth, the difference between maternal and fetal plasma glucose concentrations remains very small (~9 mg/dL; 0.5 mmol/L).[28]

## TRANSITIONAL NEONATAL HYPOGLYCEMIA IN NORMAL NEWBORNS

### PATTERN OF PLASMA GLUCOSE CONCENTRATIONS IN NORMAL NEWBORNS AFTER BIRTH

Figure 153-3 illustrates the changes in mean glucose concentrations in newborn infants during the transition from intrauterine to extrauterine life (similar data have been reported in many other cross-sectional studies[29-31]). In normal newborns, the mean plasma glucose concentration quickly falls from levels before delivery that are close to maternal glucose levels and are similar to the normal levels of infants, children, and adults (~80 mg/dL); the mean glucose concentration quickly drops by 1 to 2 hours after delivery to reach a nadir of approximately 60 mg/dL before rising by the second or third day after birth back into the normal range of 70 to 100 mg/dL for children and adults. In addition, as seen in Figure 153-3, some high-risk newborn infants (indicated as low birth weight) have a more pronounced and more prolonged dip in plasma glucose concentrations after birth and may remain hypoglycemic for several weeks. This group of low-birth-weight infants would now be categorized as small for gestational age (SGA) as a result of intrauterine growth restriction. They illustrate a second common type of neonatal hypoglycemia associated with high-risk factors and will be discussed separately as perinatal stress hyperinsulinism or prolonged neonatal hyperinsulinism.

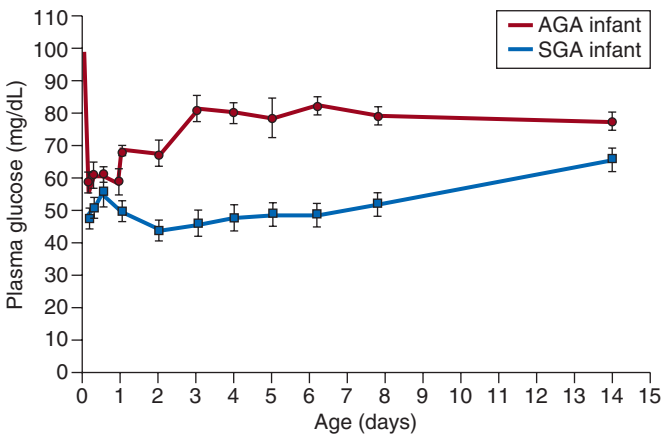


**Figure 153-3 Plasma glucose concentration in term infants during the first week of life.** Note that plasma glucose concentration has normalized to above 70 mg/dL by day 2 to day 3 in the term infant group. *AGA,* Appropriate for gestational age; *SGA,* small for gestational age. (Some data from Cornblath M, Reisner SH: Blood glucose in the neonate and its clinical significance. *N Engl J Med* 273(7):378–381, 1965.)

Figure 153-4 illustrates the distribution of plasma glucose concentrations at the nadir of transitional neonatal hypoglycemia in various groups of newborn infants before a first feeding at 8 hours of age. In 80% of the term appropriate-for-gestational-age (AGA) group, the plasma glucose concentrations dropped below the range of 70 to 100 mg/dL, which is normal for the fetus before birth and for older infants, children, and adults. The mean glucose concentration in the term AGA group was 54 mg/dL, similar to mean glucose values of 55 to 66 mg/dL immediately after birth in normal neonates in many other studies. Note that the distribution of glucose values in the term AGA group is skewed to the left by an excess of low or very low glucose values in neonates who had evidence of perinatal stress,[30] such as birth asphyxia, maternal hypertension, and low weight for length, suggesting late fetal growth deceleration—see the section entitled "Perinatal Stress Hypoglycemia (Prolonged Neonatal Hyperinsulinism)." The frequency of severe hypoglycemia was even more marked in the other groups of neonates shown in Figure 153-4, being especially high in SGA infants (perinatal stress) and in the large-for-gestational-age group (partly due to inclusion of infants with maternal diabetes). The SGA groups, in particular, show a bimodal distribution, with those having more evidence of perinatal stress also having severer hypoglycemia. Of importance, the high frequency of hypoglycemia after birth quickly resolved: whereas 36% of the term AGA neonates had glucose concentrations below 50 mg/dL at 8 hours of age, none had glucose concentrations below 50 mg/dL on days 2 and 3, and only 1% of the infants in the other groups had glucose concentrations below 50 mg/dL after the first day.

It is noteworthy that the glucose values shown in Figure 153-4 are not normally distributed. There has been a long-standing practice in neonatology of using a statistical definition of neonatal hypoglycemia. This statistical definition of hypoglycemia was based on a value two standard deviations below the mean (originally a whole-blood glucose concentration below 30 mg/dL in normal weight neonates and below 20 mg/dL in low-birth-weight neonates (i.e., plasma glucose values below 35 mg/dL and below 25 mg/dL, respectively). The fallacies involved in such statistical definitions are now well appreciated, especially because the statistical normal does not represent what is physiologically normal. As pointed out earlier in this chapter, hypoglycemia cannot be defined by any specific single value of plasma glucose concentration and, as shown later, there is no evidence that the newborn brain has any special protection against the consequences of glucose deprivation.

### PLASMA GLUCOSE CONCENTRATIONS ARE LOW BUT STABLE DURING THE PERIOD OF TRANSITIONAL NEONATAL HYPOGLYCEMIA

Although there are few longitudinal studies of plasma glucose concentrations in individual newborn infants, there is strong evidence that their low levels of plasma glucose are remarkably stable and not affected by the duration of postnatal fasting. This

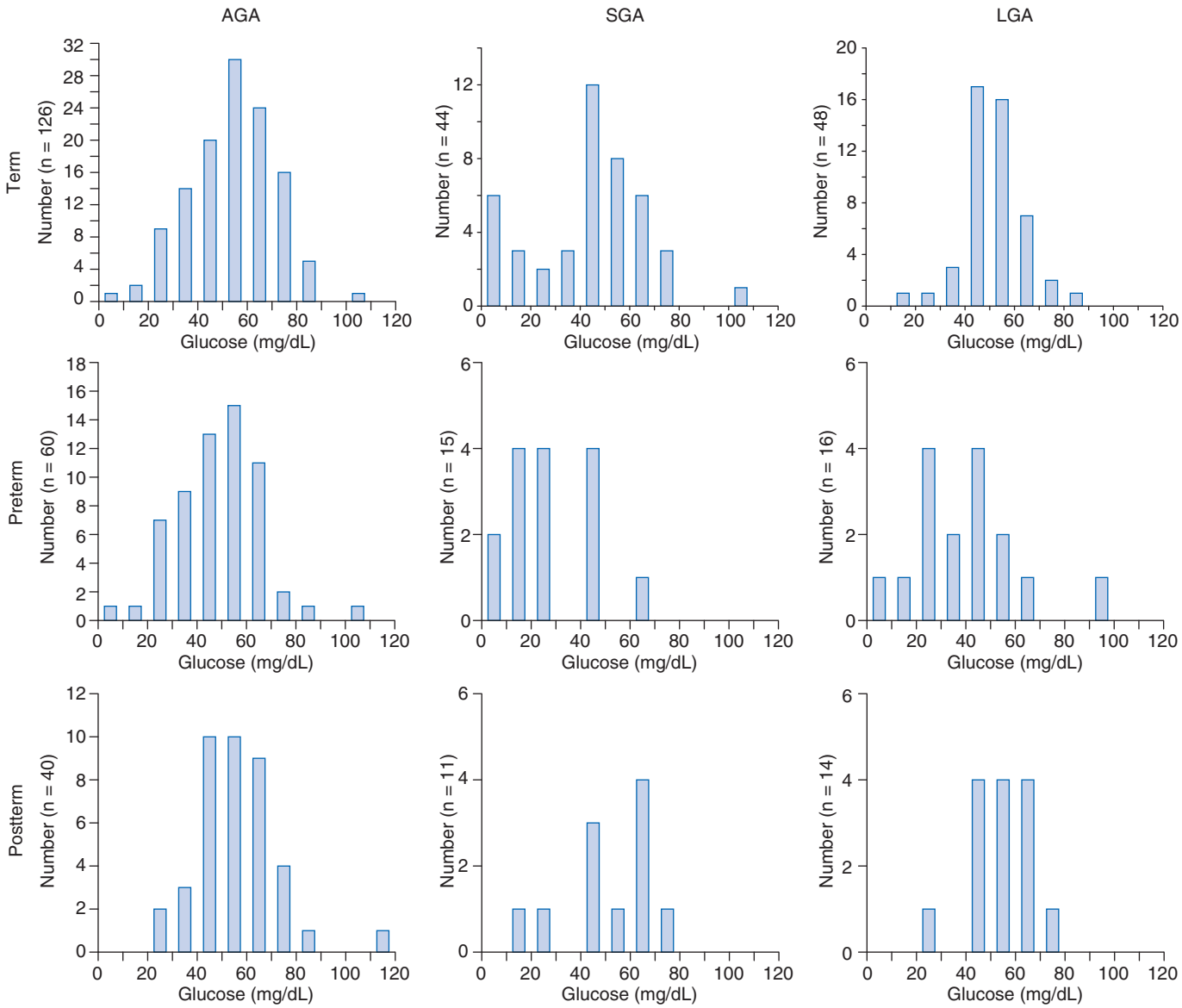


**Figure 153-4 Fasting glucose concentration at 3 to 6 hours of age.** Distribution of blood glucose concentration categorized according to gestational age (preterm, term, and postterm) and birth weight (small for gestational age [SGA], appropriate for gestational age [AGA], and large for gestational age [LGA]). Note that there is a bimodal pattern in the SGA infants, with those with lowest blood glucose concentration in this group likely having perinatal stress. (Some data from Lubchenco LO, Bard H: Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. *Pediatrics* 47(5):831–838, 1971.)

is illustrated in Figure 153-5, which shows individual glucose traces in 24 term AGA neonates before their first feeding at 8 hours after birth.[31] Despite some scatter, plasma glucose concentrations remained stable and did not appear to decline with increasing duration of fasting. The mean plasma glucose concentration at 8 hours of age (57 ± 12 mg/dL; 3.2 ± 0.7 mmol/L; mean ± standard deviation) is very similar to the mean glucose levels reported in older studies when the normal practice was to withhold feedings for 24 hours or more after delivery. In 1950, Desmond and colleagues[32] reported mean glucose levels in normal term neonates who fasted for 24 hours after birth of 57 to 69 mg/dL (2.8 to 3.3 mmol/L), which is almost identical to the level seen after fasting for only 8 hours after birth. Similarly, breast-fed neonates consume very few calories during the first few days of life, and have mean plasma glucose concentrations that are similar to those of formula-fed babies.[6,33,34]

The remarkable stability of low glucose concentrations in normal newborns on the first day after birth suggests that their transitional hypoglycemia does not reflect a block in any specific metabolic pathway (e.g., glycogenolysis, gluconeogenesis, ketogenesis). Rather, it behaves like a regulated process where the mean concentration of plasma glucose is initially maintained at 55 to 60 mg/dL immediately after birth but then increases to more than 70 mg/dL (>3.9 mmol/L) by 2 to 3 days of age. This conclusion deserves emphasis, because previous efforts to understand neonatal hypoglycemia have focused on developmental studies of enzymatic pathways in various animal models. For example, studies in rodent models have shown developmental increases in the expression or activities of the pathways of hepatic gluconeogenesis (especially phosphoenolpyruvate carboxykinase) and hepatic ketogenesis (especially carnitine palmitoyltransferase 1 and 3-hydroxy-3-methylglutaryl coenzyme A

synthase).[35,36] Most of these developmental changes occur during the first 12 hours after delivery and coincide with the transitional neonatal hypoglycemia nadir. However, deficiencies of these pathways cannot explain the glucose patterns seen in the newborn (especially because clinical experience with genetic defects in either pathway indicates that, unlike normal newborns with transitional neonatal hypoglycemia, affected patients maintain normoglycemia during fasting initially and then, only after glucose reserves are exhausted, show a rapid fall in glucose concentrations to profoundly hypoglycemic levels).

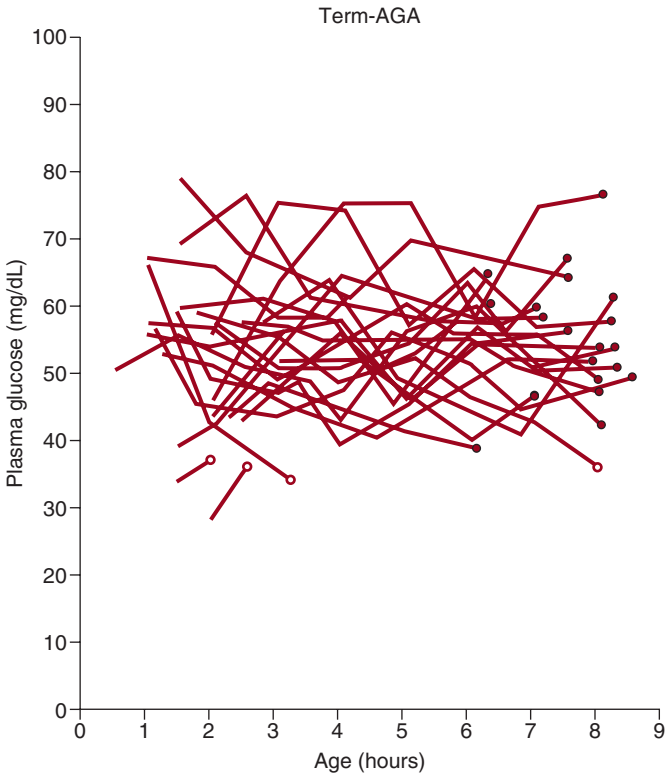


**Figure 153-5 Sequential plasma glucose concentrations during postnatal fasts in 24 term appropriate-for-gestational-age (AGA) infants.** The plasma glucose concentration of a venous sample taken at termination of the fast is shown for infants who maintained a glucose concentration of more than 40 mg/dL *(solid circles)* and for infants in whom the glucose concentration was less than 40 mg/dL *(open circles).* Despite the fasting, blood glucose concentration remained remarkably stable, although low, in these infants. (From Stanley CA, Anday EK, Baker L, et al: Metabolic fuel and hormone responses to fasting in newborn infants. *Pediatrics* 64(5):613–619, 1979.)

## TRANSITIONAL NEONATAL HYPOGLYCEMIA IN NORMAL NEWBORNS IS A HYPOKETOTIC HYPOGLYCEMIA.

The fasting systems approach outlined in Figure 153-2 has been applied in three separate studies of hypoglycemia in normal newborns that provide insight into the mechanism of transitional neonatal hypoglycemia. The data show that hypoglycemia is associated with suppressed plasma concentrations of ketones (β-hydroxybutyrate and acetoacetate) during the first 1 to 2 days of life.[31,37] This is illustrated in Table 153-1 by data from Stanley and colleagues[31] on fuel responses to hypoglycemia in groups of normal neonates compared with the normal responses to fasting hypoglycemia seen in older children and with the responses seen in children with hypoglycemia due to hyperinsulinism. Note that both the neonates with severe hypoglycemia (<40 mg/dL) and those with milder hypoglycemia (61 ± 2 mg/dL, mean ± standard error of the mean) had mean levels of total ketones that were 10-fold lower than those of hypoglycemic normal children (0.37 mmol/L and 0.18 mmol/L compared with 2.7 mmol/L). Similar data showing suppression of ketone levels during hypoglycemia on the first day after birth in normal newborns have been reported by Hawdon and colleagues[37] and Haymond and colleagues,[38] and data have also been reported showing low levels of ketones during hypoglycemia in SGA and other groups of neonates by several groups.[31,39,40] Because ketone production by the liver and utilization by the brain are both linearly related to plasma concentrations, these very low levels of ketones indicate a marked suppression of ketogenesis. The low levels also highlight the fact that ketones cannot compensate as a fuel for the brain when newborns are hypoglycemic. As shown in Figure 153-6, the inability to increase ketone production during hypoglycemia is a feature of SGA and premature neonates, as well as normal term AGA infants.

Parenthetically, it should be noted that surveys of ketone levels in neonates over the first weeks of life have demonstrated mild increases in plasma levels on days 3 to 5 after birth in breast-fed but not formula-fed neonates. Originally, this was interpreted as a "suckling ketosis," similar to what occurs in rodents and some other species because of the their high milk fat content. However, the transient elevation of ketone levels in breast-fed

**Table 153-1 Response of Normal Neonates to an 8-Hour Fast After Delivery (Mean ± Standard Error of the Mean)**

| | | | Controls | |
|---|---|---|---|---|
| | Term, AGA (*n* = 20) (Glucose >40 mg/dL) | Term, AGA (*n* = 4) (Glucose <40 mg/dL) | Normal Children (*n* = 7) (After 24 hr of Fasting) | Hyperinsulinism (*n* = 7) (When Hypoglycemic) |
| Length of fasting (hr) | 7.6 ± 0.1 | 3.8 ± 1.4 | 24 | 6.4 ± 1.9 |
| Plasma glucose (mg/dL) | 61 ± 2 | 38 ± 1.4 | 52 ± 4.5 | 29 ± 5 |
| β-Hydroxybutyrate (mmol/L) | 0.31 ± 0.04 | 0.16 ± 0.03 | 2.5 ± 0.5 | 0.6 ± 0.2 |
| Acetoacetate (mmol/L) | 0.06 ± 0.01 | 0.02 ± 0.01 | 0.2 ± 0.1 | 0.1 ± 0.08 |
| Free fatty acids (mmol/L) | 1.4 ± 0.07 | 1.3 ± 0.23 | 1.6 ± 0.2 | 0.5 ± 0.2 |
| Plasma insulin (μU/mL) | 10 ± 0.9 | 7.9 ± 1.3 | 6.8 ± 1.3 | 15 ± 3.5 |

Modified from Stanley CA, Anday EK, Baker L, et al: Metabolic fuel and hormone responses to fasting in newborn infants. *Pediatrics* 64(5):613–619, 1979.
*AGA,* Appropriate for gestational age.
This demonstrates the differences in fuel metabolism between the term AGA infant and the older child during hypoglycemia. Note that β-hydroxybutyrate production is suppressed in the AGA infant during hypoglycemia in comparison with the normal older child.

human infants is most likely due to a combination of their not yet having achieved full calorie intake, together with resolution of transitional neonatal hyperinsulinism.

As shown in Figure 153-2, *B,* the feature of low ketone levels during transitional neonatal hypoglycemia could be due to either a defect in hepatic fatty acid oxidation or hyperinsulinism. As discussed later, other data on liver glycogen reserves and on plasma insulin levels are most consistent with hyperinsulinism being the mechanism responsible, rather than a defect in the pathways of fatty acid oxidation.

## TRANSITIONAL NEONATAL HYPOGLYCEMIA IS ASSOCIATED WITH INAPPROPRIATE CONSERVATION OF LIVER GLYCOGEN STORES

Normally during fasting, liver glycogen stores should become depleted before plasma glucose concentration falls to the level of hypoglycemia. The glycemic response to administration of glucagon or epinephrine can be used to estimate liver glycogen reserves. Thus a glycemic response to glucagon injection of more than 30 mg/dL at a time of hypoglycemia provides evidence of an inappropriate liver glycogen reserve and, as shown in Figure 153-2, *B,* provides a simple test for confirmation of hyperinsulinism.[25]

In 1950 Desmond and colleagues[32] studied the glycemic response to epinephrine in normal infants during the first several days after birth. During the first 24 hours after delivery, no feedings were given, according to the usual practice at that time. At 24 hours of age, epinephrine produced a brisk rise in glucose levels from a mean of approximately 50 mg/dL to a mean of approximately 85 mg/dL.[32] Similar brisk glycemic responses have been reported in normal newborns with use of glucagon as a stimulus for glycogenolysis[41,42] and also in hypoglycemic premature and SGA infants.[43,44] These studies of the glycemic response to glucagon and epinephrine in newborn infants during the first 2 days after birth provide evidence that insulin is the mechanism of transitional neonatal hypoglycemia in normal newborns.

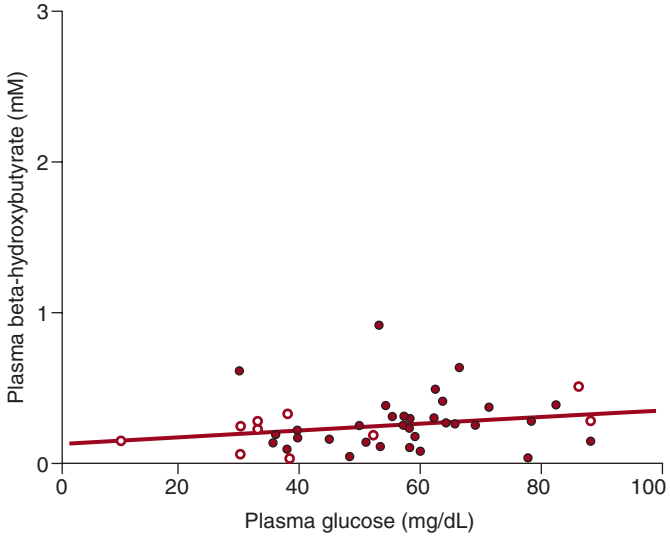


**Figure 153-6 Plasma glucose and β-hydroxybutyrate levels at the end of postnatal fasts in appropriate-for-gestational-age infants *(solid circles)* and small-for-gestational-age infants *(open circles).*** In the first 8 hours after birth, these infants had suppressed ketone levels during hypoglycemia. (From Stanley CA, Anday EK, Baker L, et al: Metabolic fuel and hormone responses to fasting in newborn infants. *Pediatrics* 64(5):613–619, 1979.)

## INSULIN SECRETION IS NOT COMPLETELY SUPPRESSED DURING TRANSITIONAL NEONATAL HYPOGLYCEMIA

As shown in Table 153-1, plasma insulin concentrations were slightly higher in the groups of term AGA neonates than in the control group of normal older children with hypoglycemia. Figure 153-7 provides further evidence that insulin secretion is suppressed at lower glucose levels in neonates compared with older children (see Figure 153-7).[45] Whereas insulin levels in normal children were suppressed completely at plasma glucose concentrations below 4.0 to 4.5 mmol/L (70 to 75 mg/dL), complete suppression of insulin secretion did not occur in term and preterm neonates until plasma glucose levels were below 2 to 3 mmol/L (35 to 55 mg/dL). These data are also consistent with a study of basal and glucose-stimulated insulin secretion in normal newborns immediately after delivery, which indicated that portal vein insulin concentrations were not suppressed (49 ± 29 μU/mL) at a mean plasma glucose concentration of 44 ± 20 mg/dL[46]; this contrasts with the finding in older infants, in which portal vein insulin levels were normally suppressed at glucose levels of 35 to 50 mg/dL. Note that plasma insulin levels at times of hypoglycemia are not dramatically elevated in neonates but the same is also true of infants with congenital hyperinsulinism (Table 153-1).[47,48] Therefore the problem with insulin secretion in congenital hyperinsulinism is not primarily due to hypersecretion but rather is due to a failure to turn off insulin secretion adequately at low glucose levels; this is also true during transitional neonatal hypoglycemia in normal newborns.

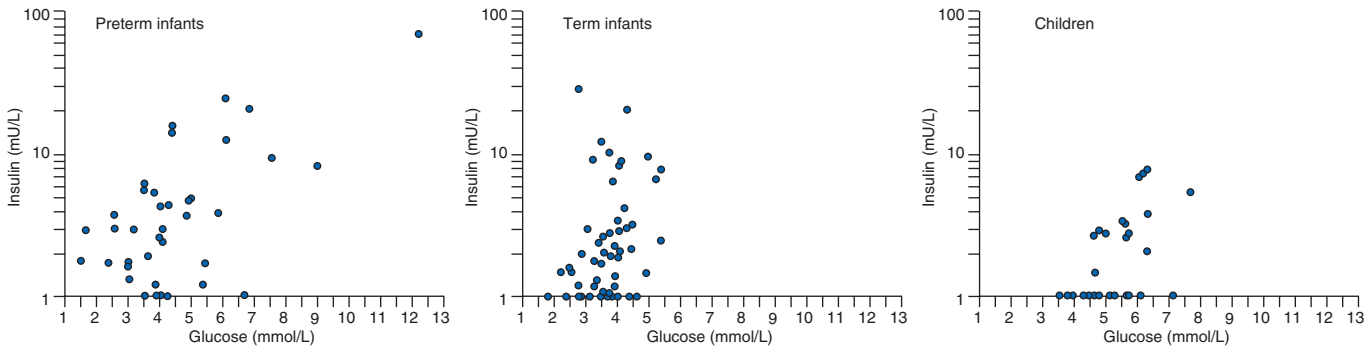


**Figure 153-7 Insulin and glucose concentrations in term and preterm infants and in older children.** Older children had suppressed insulin secretion at a plasma glucose level of 4.5 mmol/L (80 mg/dL) but the glucose threshold for suppressed insulin secretion in term infants was lower. In preterm infants, insulin secretion was detected at a glucose level as low as 1.5 mmol/L (30 mg/dL). (From Hawdon JM, Aynsley-Green A, Ward Platt MP: Neonatal blood glucose concentrations: metabolic effects of intravenous glucagon and intragastric medium chain triglyceride. *Arch Dis Child* 68(3 Spec No):255–261, 1993.)

## SUMMARY OF THE MECHANISM OF TRANSITIONAL NEONATAL HYPOGLYCEMIA IN NORMAL NEWBORNS

The cardinal features of transitional neonatal hypoglycemia in normal term AGA newborns (stable hypoglycemia unaffected by feeding or fasting, low levels of plasma ketones, incomplete suppression of plasma insulin levels, and inappropriately large glycemic responses to glucagon or epinephrine) are similar to those seen in a genetic form of hyperinsulinism caused by activating mutations of glucokinase.[49] Glucokinase plays a key role in determining the beta-cell glucose threshold for insulin secretion. Heterozygous activating mutations of glucokinase lower the glucose threshold for insulin release such that baseline concentrations of plasma glucose in affected patients are maintained in the range of 55 to 65 mg/dL (2.8 to 3.6 mmol/L). These low glucose levels are relatively resistant to change and remain fairly constant in both the fed and the fasted state. With prolonged fasting, patients with glucokinase mutations may even begin to develop hyperketonemia if their glucose levels remain low for long enough to completely suppress insulin secretion. Because their glucose setpoint is close to the glucose thresholds for neurogenic and neuroglycopenic responses, individuals with glucokinase hyperinsulinism have frequent mild symptoms of hypoglycemia; however, they have a lower risk for brain damage than individuals with other forms of hyperinsulinism in which more extreme degrees of hypoglycemia are likelier. This may explain why transitional neonatal hypoglycemia, in which glucose levels are also close to the thresholds for symptoms in older children and adults, is unlikely to produce permanent brain damage in normal newborns.[49,50]

## BRAIN RESPONSES TO TRANSITIONAL NEONATAL HYPOGLYCEMIA

It has often been assumed that the brain is resistant to the effects of hypoglycemia during the newborn period. Studies of susceptibility to brain damage from hypoglycemia in the newborn period versus later in life in experimental animals have reached conflicting conclusions.[51,52] As emphasized earlier, normal newborns are unable to generate any alternative fuel that might serve as protection for the brain during hypoglycemia (i.e., ketones). In addition, some reports suggest that the neurophysiologic responses during transitional hypoglycemia are similar to the responses to hypoglycemia at older ages. For example, there appear to be increases in the levels of counterregulatory hormones (e.g., epinephrine and glucagon) in neonates[17] that are comparable to those in older children and adults.[18] This suggests that the threshold for brain neurogenic (i.e., neuroendocrine) responses to glucose deprivation may be similar across all ages. Furthermore, there is no reason to assume that the neonatal brain can tolerate lower blood glucose levels than the older infant, child, or adult.

Whether or not there are adverse consequences of transitional neonatal hypoglycemia in the first 24 hours of life in normal term AGA infants is not known and requires further investigation. The transient hypoglycemia that is common in normal neonates is not thought to have long-term effects, possibly because the nadir remains above the threshold for neuroglycopenic responses. However, a recent study by Kaiser and colleagues[53] challenges the assumption that transient neonatal hypoglycemia is always benign. In their study using data from a statewide fourth-grade school examination, they found that neonates with a single plasma glucose level below 40 mg/dL had a 50% lower odds ratio for proficiency in both literacy (0.43, 95% confidence interval [CI] 0.28 to 0.67) and mathematics (0.51, 95% CI 0.34 to 0.78); those with a single plasma glucose level below 35 mg/dL had even lower odds ratios for proficiency in literacy (0.49, 95% CI 0.28 to 0.83) and mathematics (0.49, 95% CI 0.29 to 0.82). Even infants with a single plasma glucose level below a cutoff as high as 45 mg/dL had a reduced odds ratio for proficiency in literacy (0.62, 95% CI 0.45 to 0.85) but not mathematics (0.78, 95% CI 0.57 to 1.08).

In cases of severer hypoglycemia, however, permanent brain injury can occur. For example, in a group of 158 newborns with blood glucose concentrations below 30 mg/dL), Koivisto and colleagues[54] reported normal development in only 38% of infants who had a hypoglycemic seizure. In contrast, development was normal in 77% of infants with other symptomatic hypoglycemia, and in 80% of those with asymptomatic hypoglycemia, whereas development was normal in 91% of infants with glucose levels above 30 mg/dL. At the severest end of the spectrum of neonatal hypoketotic hyperinsulinemic hypoglycemia, in children with persistent congenital hyperinsulinism, very high rates of developmental delay (21% to 44%) and epilepsy (18% to 25%) have been reported.[1,2] Thus in newborns the brain is sensitive to hypoglycemia, and early recognition and adequate treatment of those with disorders of hypoglycemia is of great importance.

## FUTURE AREAS OF INVESTIGATION IN TRANSITIONAL NEONATAL HYPOGLYCEMIA

The available evidence on the phenomenon of transitional neonatal hypoglycemia in normal neonates indicates that it represents a mild form of hyperinsulinism in which the glucose threshold for insulin secretion is set at a lower level of glucose for the first 1 to 2 days after birth. This may be an important adaptation during fetal life, because having a much lower glucose threshold than its mother may allow the fetus to maintain high rates of insulin secretion to support growth, especially during times when maternal glucose levels may be low (e.g., preprandial or overnight fasting). The mechanisms responsible for the apparent lower pancreatic islet glucose threshold in the fetus are not known. However, recent data from studies of islets from fetal and neonatal rodent models suggest at least one possible explanation for further study. The glucose threshold for insulin release is lower in islets isolated from newborn rats on postnatal day 1 (2.8 mmol/L) than in islets from mature rats.[55] In newborn mice, Thorrez and colleagues[56] found expression of two genes, a plasma membrane pyruvate/lactate transporter and lactate dehydrogenase, which are normally disallowed from mature beta cells in order to restrict the types of fuels that can elicit release of insulin. Mature beta cells do not express these two genes and therefore are unresponsive to the rise in lactate and pyruvate levels that occurs with anaerobic exercise. For example, a genetic form of hyperinsulinism, caused by mutations in the promoter region of the pyruvate/lactate transporter, is associated with episodes of hypoglycemia during exercise. The studies of Thorrez and colleagues[56] showed that expression of the lactate/pyruvate carrier and that of lactate dehydrogenase are both increased several-fold in islets from postnatal day 1 newborn mice compared with mature islets and then quickly fall to adult levels by postnatal days 2 and 3. A similar change in islet gene expression could explain the phenomenon of transitional neonatal hypoglycemia and its rapid resolution by 2 to 3 days after birth in human newborns. Further studies of the mechanisms that control the changes in islet regulation of insulin secretion during the fetal to newborn transitional period and of the signals that allow rapid maturation of islet function during the first 1 to 3 days of life are needed.

# PERINATAL STRESS HYPOGLYCEMIA (PROLONGED NEONATAL HYPERINSULINISM)

In contrast to transitional neonatal hypoglycemia, which is mild and usually of very short duration, some groups of newborns are at high risk for developing a severer and more prolonged form

of hypoglycemia, which can persist for several weeks after birth before resolving. This is illustrated in Figure 153-4 with data from Lubchenco and Bard,[30] where severe low plasma glucose levels were associated with evidence of perinatal stresses, including late intrauterine growth retardation and birth asphyxia. Similarly, in Figure 153-3, the group labeled as low birth weight (i.e., *SGA*) had lower mean glucose levels, which lasted for several weeks after birth.[5]

Severe and prolonged hypoglycemia in high-risk neonates, known to be caused by hyperinsulinism since the 1980s, is commonly referred to as either *perinatal stress hypoglycemia* or *prolonged neonatal hyperinsulinism.* Collins and Leonard[57] first described perinatal stress hyperinsulinism in 1984 in a group of six neonates, three of whom had perinatal hypoxia and the other three were small for their gestational age. These infants had severe hypoglycemia and symptoms, including seizures, and diagnostic features of hyperinsulinism; their hypoglycemia was controllable with diazoxide, a drug that suppresses insulin release, and eventually resolved after several weeks. These authors subsequently described additional cases of SGA neonates with severe hyperinsulinism who required diazoxide treatment for several weeks to control their hypoglycemia before it resolved. In 2006 Hoe and colleagues[58] described a similar group of 26 infants with prolonged neonatal hyperinsulinism. As shown in Table 153-1, associated risk factors included male sex (81%), caesarean delivery (62%), perinatal stress (35%), poor intrauterine growth (27%), prematurity (23%), and maternal hypertension (12%). In one fifth of the infants no specific perinatal stresses or risk factors were identified. Infants with erythroblastosis fetalis are also known to be at high risk for transient hyperinsulinemic hypoglycemia at birth, which may be secondary to perinatal hypoxia due to their extreme anemia.[59-61]

Perinatal stress hypoglycemia/prolonged neonatal hyperinsulinism is a relatively common occurrence in the newborn period and much more common than genetic or syndromic forms of hypoglycemia, which are described later. Mizumoto and colleagues,[62] in Japan, have described cases of perinatal stress hypoglycemia/prolonged neonatal hyperinsulinism occurring among approximately 10% of infants admitted to a neonatal intensive care unit. Palloto and Simmons[63] have estimated that perinatal stress hypoglycemia persists beyond 1 week after birth in 8% of SGA infants.

The clinical severity and duration of hyperinsulinism in infants with prolonged neonatal hyperinsulinism is variable and not predicted by the degree of perinatal stress. Although a mechanistic link between hyperinsulinism in perinatal stress and transitional neonatal hypoglycemia has not been established, it is tempting to speculate that the two share a common mechanism and that perinatal stresses simply cause a prolongation of the normal period of transitional hyperinsulinism after birth. Although most cases of perinatal stress hypoglycemia respond well to diazoxide treatment, some of the severer cases may have extremely high glucose requirements and may not respond to diazoxide. In these exceptional cases, support with supplemental glucose may be required for a prolonged period after birth.

## PERMANENT DISORDERS OF HYPOGLYCEMIA THAT PRESENT IN THE NEONATE

This section will briefly review the most common types of chronic hypoglycemia disorders that can present in the newborn period: genetic and syndromic forms of congenital hyperinsulinism and congenital pituitary deficiency. It is extremely important to identify patients with these hypoglycemia disorders before their discharge, because they are at very high risk for seizures and brain injury, especially if diagnosis and treatment are delayed.[2] Transitional neonatal hypoglycemia may interfere with recognition of these disorders during the first 1 to 2 days after birth. However, by the third day after birth, plasma glucose concentrations and insulin secretion in normal newborns should be similar to the normal range for older children, and evaluation and treatment should be considered for any neonate with recurrent hypoglycemia that persists beyond 2 to 3 days of age.

### GENETIC FORMS OF CONGENITAL HYPERINSULINISM

The incidence of the severe form of congenital hyperinsulinism ranges from an estimated 1 in 40,000 births in Europe to 1 in 2,500 births in Saudi Arabia; if the milder forms of hyperinsulinism are included, the total incidence may be as high in 1 in 10,000 to 1 in 20,000 births. Congenital persistent hyperinsulinism is both clinically and genetically heterogeneous. The clinical heterogeneity ranges from extremely severe, life-threatening disease to very mild clinical symptoms, which may sometimes be difficult to identify. Furthermore, clinical responsiveness to medical and surgical management is variable and genotype specific.[64]

The genetic causes of congenital hyperinsulinism continue to be elucidated. As shown in Figure 153-8, 10 different genetic loci have been associated with congenital hyperinsulinism. These occur in the major pathways for triggering insulin secretion by the major nutrients, glucose, and amino acids. Some of the mutations are recessive but some are dominant and frequently sporadic rather than familial. The most frequent causes of congenital hyperinsulinism are inactivating mutations in either of the two subunits of the beta-cell adenosine triphosphate (ATP)-sensitive potassium channel ($K_{ATP}$ channel), sulfonylurea receptor encoded by *ABCC8*, and Kir6.2 (an inward-rectifying potassium channel) encoded by *KCNJ11*.[65] The second most common mutations associated with hyperinsulinism are dominant gain-of-function mutations of glutamate dehydrogenase 1 (encoded by *GLUD1*), which causes a diazoxide-responsive protein-sensitive form of hyperinsulinism associated with persistent hyperammonemia (hyperinsulinism-hyperammonemia syndrome). The third most common genetic form of congenital hyperinsulinism is associated with dominant activating mutations of glucokinase (encoded by *GCK*) and is often not responsive to diazoxide. The other genetic loci shown in Figure 153-8 are much rarer and each accounts for only 1% to 2% of the total number of hyperinsulinism cases.[66-69] In as many as 50% of the cases of congenital hyperinsulinism, no genetic defect has been demonstrated.[70]

The mainstay of medical therapy for congenital hyperinsulinism is diazoxide, which activates the $K_{ATP}$ channel to suppress insulin release (see Figure 153-8). In most patients with hyperinsulinism due to mutations in either of the two subunits of the $K_{ATP}$ channel, diazoxide has no effect, and many will require near-total pancreatectomy to control hypoglycemia. Of special importance, about half of patients with diazoxide-unresponsive hyperinsulinism may have a surgically curable focal form of hyperinsulinism. These focal lesions of islet adenomatosis are caused by a loss of the maternal chromosomal 11p region in combination with a paternally transmitted recessive $K_{ATP}$ channel mutation.

In addition to the congenital forms of hyperinsulinism associated with genetic defects in the pathways of insulin secretion shown in Figure 153-8, several syndromes associated with hyperinsulinism may present in newborn infants. These include Beckwith-Wiedemann syndrome, which is associated with large-for-gestational-age birth weight, hemihypertrophy, organomegaly, large tongue, umbilical hernia, and earlobe creases. Approximately half of infants with Beckwith-Wiedemann syndrome have hyperinsulinemic hypoglycemia of variable severity and duration from birth. Although some may be responsive to diazoxide, some (particularly those with mosaic isodisomy for the paternally derived 11p region) may

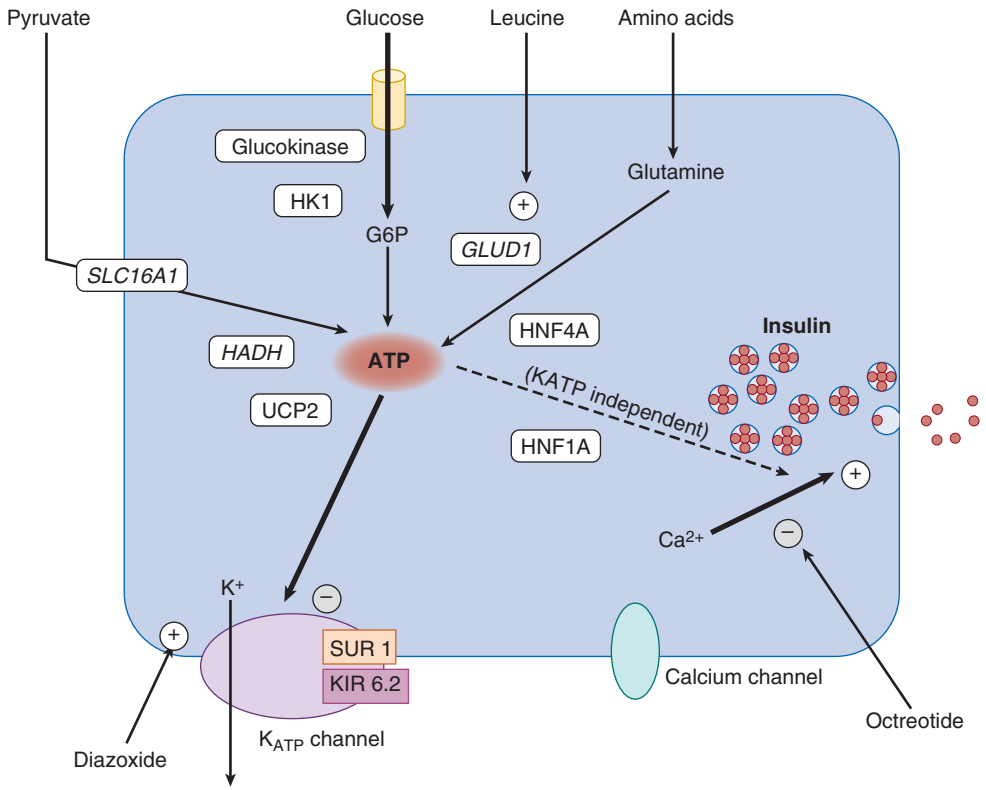


**Figure 153-8 Substrate-mediated insulin secretion from the pancreatic beta cell.** Glucose stimulates insulin secretion through its oxidation, which increases the levels of intracellular adenosine triphosphate (ATP), which in turn inhibits the potassium efflux through the ATP-sensitive potassium channel ($K_{ATP}$ channel) (the sulfonylurea receptor [SUR 1]-inward rectifying potassium channel [KIR] protein complex). Closure of the $K_{ATP}$ channel depolarizes the plasma membrane, which activates the voltage-gated calcium channel to increase intracellular calcium concentration and to trigger exocytosis of insulin granules. Mutations causing genetic hyperinsulinism are shown as a *black-bordered box. G6P,* Glucose 6-phosphate.

have very severe hyperinsulinism that does not respond to diazoxide and may persist for several years after birth. Other syndromes associated with hyperinsulinism include Kabuki makeup syndrome, Turner syndrome, and some of the congenital disorders of glycosylation.

## CONGENITAL HYPOPITUITARISM

The clinical presentation of neonates with panhypopituitarism can include features of severe hypoglycemia that are identical to those seen in congenital hyperinsulinism. These include a high glucose requirement to maintain euglycemia, inappropriate hypoketonemia, and a positive glycemic response to glucagon at the time of hypoglycemia. Plasma insulin concentrations may be elevated or normal. The hyperinsulinism may represent a form of perinatal stress–induced hyperinsulinism, because hypoglycemia seen with pituitary deficiency in older infants and children is usually associated with hyperketonemia (see Figure 153-2, *B*). Usually the pituitary deficiency associated with neonatal hypoglycemia includes multiple deficiencies of cortisol and growth hormone, with or without concomitant secondary hypothyroxinemia. The hyperinsulinemic hypoglycemia of neonatal panhypopituitarism responds poorly to treatment with diazoxide but is readily controlled by treatment that replaces all of the deficient hormones (including thyroxine, in addition to cortisol and growth hormone). Physical features such as micropenis or midline facial malformations such as cleft palate or microphthalmia should suggest the possibility of pituitary deficiency as the cause of neonatal hypoglycemia, but some patients may not have abnormal physical features.[71] Neonatal hypopituitarism is sometimes associated with cholestatic jaundice; which often may not improve until hormone deficiencies have been treated.[72]

Low cortisol or growth hormone concentration during hypoglycemia is not sufficient for a diagnosis of deficiency of these hormones[26]; specific stimulation testing of these hormones is recommended if there is clinical suspicion. In states where only thyroid-stimulating hormone concentrations and not thyroxine concentrations are measured, central hypothyroidism may not be detected on the newborn screen.

## SUMMARY

Prompt recognition and treatment of hypoglycemia disorders in neonates is essential to prevent the possibility of seizures and permanent brain injury. This is complicated by the need to consider three broad categories of hypoglycemia immediately after birth. The first is transitional neonatal hypoglycemia, which is common to all normal newborns and reflects persistence of the fetal pattern of insulin regulation; the hypoglycemia is usually mild and fully resolves within 2 to 3 days after birth. The second is perinatal stress–induced hypoglycemia, which is a severer and more prolonged period of hyperinsulinemic hypoglycemia that is commonly associated with perinatal stresses such as intrauterine growth restriction, birth asphyxia, and maternal preeclampsia; this may reflect an exaggeration of transitional neonatal hyperinsulinism, but some cases can require treatment for weeks to months after birth. The third category includes the congenital or genetic disorders of hypoglycemia that will require lifelong

treatment, and in which achievement of sustained normoglycemia may be very difficult or impossible. Although there is a long list of such disorders, the genetic and syndromic forms of congenital hyperinsulinism and congenital hypopituitarism are the most urgent to recognize before discharge of the infant from the nursery. During the first 2 days after birth, it may be difficult to determine in which category an infant belongs. However, a determination usually becomes feasible by 2 to 3 days of age, and should be made before discharge of the infant from the nursery.

Complete reference list is available at www.ExpertConsult.com.

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