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Knowledge Gaps and Research Needs for Understanding and Treating Neonatal Hypoglycemia: Workshop Report from Eunice Kennedy Shriver National Institute of Child Health and Human Development

William W. Hay Jr., MD, **Tonse NK. Raju, MD, DCH**, **Rosemary D. Higgins, MD**, **Satish C. Kalhan, MBBS, FRCP**, and **Sherin U. Devaskar, MD**
Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO (W.H.); Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD (T.R., R.H.), the Department of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH (S.K.), and the Department of Pediatrics, David Geffen School of Medicine, University of California Los Angeles & Mattel Children's Hospital UCLA, Los Angeles, CA (S.D.)

Maintenance of glucose homeostasis via initiation of glucose production is one of the critical physiological events that results in a smooth transition and adaptation to extrauterine life. A number of neonates have difficulty during transition to the extrauterine environment that result in altered glucose homeostasis and low plasma glucose concentrations. Although much progress has been made over the years in understanding the causes and mechanisms of altered neonatal glucose metabolism, the long-term consequences and the threshold values that may cause injury remain unknown. In 2000, Cornblath et al summarized the contemporary state of knowledge related to neonatal hypoglycemia by noting the following:

> Unfortunately, untoward long-term outcomes in infants with one or two low blood glucose levels have become the grounds for litigation and for alleged malpractice, even though the causative relationship between the two is tenuous at best… The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology.[1]

There has been no substantial evidence-based progress in defining what constitutes clinically significant but transient neonatal hypoglycemia (as opposed to persistent hypoglycemia from hyperinsulinemia), particularly regarding how it relates to brain injury. Monitoring for and prevention and treatment of neonatal hypoglycemia remain largely empirical.

At present there is neither a rational basis nor sufficient evidence to identify a specific value or a range of plasma glucose concentrations that would define “hypoglycemia” as a pathologic entity. Nevertheless, many commentaries and opinions continue to recommend various plasma glucose concentrations that should be maintained in the neonatal period to prevent injury to the developing brain.[2-9] Most published statements and opinions are based on low-level evidence, including small-scale human studies in select populations without control subjects or longer-term follow-up, case studies of neonates with a potpourri of diagnoses, or physiological or animal studies of limited relevance to human newborns. No definition of pathologic hypoglycemia or guideline for treatment of low plasma glucose

Reprint requests: Tonse N. K. Raju, MD, DCH, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, 6100 Executive Blvd, Room 4B03, Bethesda, MD, 20892. rajut@mail.nih.gov.

concentrations in neonates has been validated in clinical practice or assessed in prospective follow-up studies.

Recognizing the common occurrence of low plasma glucose, usually noted as <40 to 45 mg/dL and occurring in as many as 5% to 15% of normal newborn infants,[1,10] the potential for insufficient glucose supply to injure the developing brain, and a need to support research targeted at gaps in knowledge about neonatal "hypoglycemia" and its clinical implications, the Eunice Kennedy Shriver National Institute of Child Health and Human Development convened a workshop on Neonatal Hypoglycemia, held September 8-9, 2008. A diverse group of experts participated.

This report provides a summary of the workshop discussions. Because review articles have addressed specific hypoglycemic syndromes and several of the major themes addressed in this workshop,[11-17] the following summary will focus on gaps in knowledge and suggested research. Unless otherwise stated, "hypoglycemia" refers to "neonatal hypoglycemia" and "blood glucose" concentrations to plasma values (or whole blood glucose concentrations corrected to plasma values), expressed in millimoles per liter with mg/dL in parenthesis. The workshop did not address the so-called *persistent hypoglycemic syndromes* caused by, for example, hyperinsulinemic hypoglycemia;[18-25] hypoglycemia caused by fatty acid oxidation defects,[26,27] and other inborn errors of metabolism, which been well characterized.[28] Instead this review focuses on specific issues related to low plasma glucose concentrations in the first several hours or days after birth and their measurement, clinical monitoring, and long-term consequences.

Objectives of the Workshop

The objectives of the workshop were to identify major gaps in knowledge related to neonatal hypoglycemia and not to develop a "consensus" on either its definition or treatment. The participants were asked to propose a research agenda that, if successfully completed, might help address key issues on this topic, such as how to define clinically significant hypoglycemia; how to monitor glucose concentrations in newborn infants; how best to prevent and treat neonatal hypoglycemia; and how to determine the effects of different plasma glucose concentrations and supply of glucose to the brain on long-term neurologic outcomes. The discussion topics focused on 3 interrelated fields: (1) basic science topics on fetal and neonatal glucose homeostasis and the neurobiology of substrate use by the developing brain for energy metabolism; (2) defining clinically significant hypoglycemia; and (3) monitoring and treatment of low plasma glucose.

Fetal and Neonatal Glucose Metabolism

The fetus depends entirely on maternal supply and placental transfer of glucose, amino acids, free fatty acids, ketones, and glycerol for its energy needs. The normal lower limit of fetal glucose concentration remains around 3 mmol/L (54 mg/dL) over most of gestation, particularly after 20 weeks.[29,30] There is no fetal glucose production under normal conditions; in most cases, gluconeogenesis appears only after birth, although it has been produced in animal models with prolonged periods (days to weeks) of abnormally low glucose supply.[31,32]

After birth and clamping of the umbilical cord, neonatal glucose concentration decreases rapidly but to varying degree in all infants, rebounding to higher values within 2 to 3 hours.[33,34] These changes in glucose concentration are modified by a number of factors, including prior fetal glucose homeostasis influenced by antepartum and peripartum events, umbilical concentrations of glucose, plasma insulin concentrations, and the onset of neonatal glucose production from glycogenolysis and gluconeogenesis. There is considerable variability in

glucose concentrations during this early postnatal period, both within individual neonates and among groups of neonates of different gestational ages and growth patterns.

In most term infants who are formula fed, glucose concentration exceeds 2.2 mmol/L (40 mg/dL) by 6 to 12 hours of postnatal age. Infants exclusively breastfed tend to have lower blood glucose concentrations than those fed infant formulas.[12,17,29,30,33,34] Swenne et al[35] observed that in nearly one half of breastfed babies the blood glucose concentration remained below 2 mmol/L (36 mg/dL) during the first 24 hours after birth. Other studies have documented a wide range of glucose concentrations during the first 72 hours, with the lower limits as low as 1.3 mmol/L (23 mg/dL) in healthy breastfed infants. Furthermore, breastfed infants tend to have higher ketone concentrations, the principal alternate metabolic fuel for the brain.

In normal term infants, glucose production rate averages about 4 to 6 mg/kg/min, most of which is used by the brain.[36] Because of higher brain–to–body mass ratios, preterm infants and those with asymmetric growth restriction have higher weight-specific glucose production rates (~6-8 mg/min/kg) than healthy term infants.[37] About 50% of glucose used for immediate metabolism is oxidized.[38] During the first day of life, about 50% of total endogenous glucose production in term infants can be accounted for by glycogenolysis and 30% to 40% from gluconeogenesis, with glycerol primarily,[36,39-41] but also lactate and selected amino acids such as alanine as gluconeogenic substrates. Even though high fat in milk augments ketogenesis in suckling rats, the extent to which this process becomes operational in term infants consuming small amounts of breast milk has not been well studied.

Brain and Glucose Metabolism

Glucose supply to all cell types in the brain is regulated by the plasma glucose concentration and the glucose transporter 1 (GLUT1) and 3 (GLUT3) proteins. GLUT1 is expressed in the blood-brain barrier endothelial cells, astrocytes, oligodendrocytes, and choroid plexus, and GLUT3 primarily in neurons and their synaptic membranes.[42,43] GLUT 1 expression in the neonatal cerebral cortex[44] and GLUT 3 expression in the cerebellum equal those in adults.[45]

Neuronal glucose use rate is high, and whole brain glucose use accounts for most of the glucose used in the fetus and newborn. Glucose supply to the brain is essential not only under normal conditions, but also when there are conditions associated with higher energy demands, such as seizures, sepsis, and severe neonatal encephalopathy.

Low plasma glucose activates a number of counterregulatory pathways resulting in increased systemic rates of lipolysis with ketone utilization, and brain metabolism and use of alternate substrates. Even in the case of neuroglycopenia from GLUT1 deficiency syndrome, alternate fuels such as ketones ameliorate some of the neurologic symptoms.[46] Predominant alternate fuels used by the brain include pyruvate, lactate, and ketones, which are transported across membranes by the monocarboxylate transporter (MCTs) family of glycoproteins at rates sufficient to support neuronal synaptic activity. MCT1 is expressed by the endothelial cells of the blood-brain barrier, the astrocytes, oligodendrocytes, and choroid plexus; MCT4 also is noted in the choroid plexus; MCT2 is found primarily in neurons.[47,48]

There are considerable differences in regional susceptibility to hypoglycemic brain injury that contribute to the pattern and distribution of injury; however, the reported changes have not been consistent. Although animal and some neonatal imaging studies have indicated vulnerability to hypoglycemia in the occipital region, striatum, cingular cortex, and hippocampus, recent clinical and imaging studies have indicated more diverse cerebral injury in infants with significant clinical symptoms of hypoglycemia.[49,50] More research is

needed to determine the nature and distribution of regional vulnerability and their biologic basis for this phenomenon.

Brain injury from insufficient glucose supply has been shown in animal studies to consist of increased proapoptotic and apoptotic markers, necrosis, and reactive astrogliosis along with decreased antiapoptotic markers in neuronal mitochondria. Most of these investigations, however, have reported on insulin-induced hypoglycemia rather than calorie-restricted hypoglycemia, which are markedly different with respect to the use of alternate fuels. Even though some animal studies and human observations indicate worse outcome in infants with low plasma glucose or after hypoxic-ischemic conditions, mechanisms to account for this possible synergy need further investigation. Table I summarizes gaps in knowledge about the effects of low blood glucose and neuroglycopenia on brain injury that need to be addressed with future research.

Clinical Aspects

Defining Clinically Significant Hypoglycemia

With current knowledge, one cannot identify any specific concentration or range of plasma glucose concentrations that defines “significant hypoglycemia” as a pathologic entity. The so-called *operational threshold values* are useful guidelines for clinicians to take appropriate actions. However, the recommendations are not based on evidence of significant morbidity if no actions are taken. Similarly, there is no evidence that outcomes improve if actions are taken at the operational threshold value. All published definitions providing singular values or ranges have been arbitrary and developed for analytical and grouping purposes. Therefore they are not concentrations of plasma glucose for predicting brain injury or developing obligatory treatment protocols. In particular, no single plasma glucose concentration or range of glucose concentrations can be considered in isolation to predict outcome without also considering the concentrations of alternate energy substrates and associated aspects of altered physiology, metabolism, and pathologic study. Repeated and prolonged very low plasma glucose concentrations (persistent hypoglycemia), particularly associated with conditions of excessive insulin secretion, have been associated with abnormal neurologic outcome and should be investigated and treated.[12,18-25] Table II summarizes gaps in knowledge and research needs to define hypoglycemia as a pathologic entity.

Bedside Glucose Monitoring and Other Investigations

Bedside or point-of care testing for glucose is done to obtain an “estimate” of the glucose concentration quickly and conveniently in a variety of clinical situations. Although the results of such tests often are used for clinical decisions, there are several pitfalls and problems with such tests.[51-53] At present there is no point-of-care method that is sufficiently reliable and accurate in the low range of blood glucose to allow it to be used as the sole method to screen for hypoglycemia in newborn infants. There also is marked variability in obtaining and processing blood samples for analyses of glucose concentrations. Laboratory systems that provide timely results may be the preferred option; these facilities require certification by the institutional clinical pathology services and other accrediting agencies, as well as initial and ongoing assessment and maintenance of instrument function, technical training of the users, and data quality monitoring.

Thus far, there are no satisfactory methods for noninvasive monitoring of glucose or alternate substrates. Such monitoring devices, however, would have a major impact on clinical decision making. Continuous glucose monitoring with subcutaneous perfusion devices has been used to a limited extent in preterm infants.[54,55] Larger studies are required to determine the safety and effectiveness of such monitoring and to develop correlations

between blood glucose concentrations and clinical and laboratory data such as neuroimaging, electroencephalographic changes, and other measures of neural functions. Table III summarizes major gaps in knowledge and research needs to improve glucose monitoring.

Treatment Issues

There are no evidence-based guidelines that can be used for treating all newborn infants with low plasma glucose concentrations. Published guidelines of "operational thresholds" do not define "dangerous" values of glucose concentration. They only indicate that glucose concentrations are below an arbitrarily defined threshold that is based on statistical evaluations of cross-sectional data. These values are at or below the threshold value the caregiver may opt to take some action. Such actions may include retesting and continued monitoring, conducting diagnostic work-ups, or providing a quick source of glucose (eg, by oral feeding or glucose administration). The safety and efficacy of over-the-counter dextrose gels as quick sources of energy need to be tested in clinical trials.[17] As with any short-term therapy, follow-up measurements are required to determine whether the infant has been able to maintain normal glucose concentrations or needs sustained treatment. This is particularly true of infants with possible hyperinsulinism.

Infants with persistent hypoglycemia or those with inadequate responses to treatment need further evaluation. The actual threshold glucose concentrations at which treatment decisions are made have remained arbitrary. More research is needed to establish diagnostic and treatment strategies. Until such strategies are clearly defined, diagnostic and treatment approaches need to be based on available data and other leading opinions, particularly when evaluating infants with repeated or prolonged very low plasma glucose concentrations after the early postnatal period.[1,11,12,15,56,57] There is some interest in developing scoring systems for diagnosis and treatment, but at present data are insufficient to produce definitive guidelines; research to determine the value of such scoring systems should be encouraged. In infants with repeated or severe hypoglycemia, research is needed to determine the role of neuroprotective strategies, such as hypothermia and the safe introduction of alternate fuels.

Glucose profiles in preterm infants on total parenteral nutrition and those with concurrent illnesses need to be accounted for in all studies. Research is needed to predict risk on the basis of a spectrum of glucose and alternate substrate concentrations in the plasma and appropriate adjustments for postnatal age, gestational age, and specific combinations of growth at different gestational ages (small for gestational age [SGA], and large and appropriate for gestational age, respectively).

Education

Health care professionals at all levels need to be educated about glucose metabolism in the newborn infant. Such education must emphasize the need for continued research to define the characteristics of low plasma glucose, its prevention and treatment, and its actual effects on neuronal injury and later developmental outcome. Parents and the public also need to be educated about the broader aspects and major gaps in knowledge about this condition.

The clinical, logistical, and ethical constraints in the conduct of careful longitudinal studies that are required to develop correlations between plasma glucose concentrations in the newborn period and long-term developmental and neurologic outcomes should also be recognized. These should become part of the goals of education for the health care workers, parents, and the lay public. This is particularly important in light of the increasingly restrictive trends toward nonbeneficial research in institutional review boards and among health care providers. Therefore it is imperative to document the safety of the physiological

studies in the neonate, while developing safe, noninvasive technologies that are acceptable to the clinicians, parents, and society at large. Simple clinical predictive tools need to be developed, including imaging assessments, to determine clinically significant low plasma glucose levels in newborn infants. New research should be directed also at biomarkers that might help understand which infants might be at greater risk of neurodevelopmental injury and abnormal outcome, from low plasma glucose, as well as other comorbidities common to infants at risk of hypoglycemia.

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Glossary

GLUT	Glucose transporter
MCT	Monocarboxylate transporter
MRI	Magnetic resonance imaging

SGA	Small for gestational age

Table I

Glucose metabolism and the brain

General gaps in knowledge

The complex nature and maturational features of global and regional brain energy use remain to be studied in human neonates.

Research agenda

Define “brain energy sufficiency” by identifying the key indicators that are altered when levels of adenosine triphosphate and phosphocreatine decrease.

Determine plasma glucose concentrations that adversely affect brain functions under different conditions (eg, SGA, infants of diabetic mothers; neonatal encephalopathy, seizures, sepsis)

Determine brain cellular use of alternate fuels (eg, lactate, ketone bodies), as well as alternate fuel production under conditions of diminished glucose availability with physiological and genetically altered animal models.

Determine the relationship between plasma concentrations of energy substrates on brain structure and function, with such techniques as imaging, mass spectroscopy and ^{1}H, ^{31}P nuclear magnetic resonance spectroscopy; and longitudinal phenotypic evaluations in genetically-modified animal models and in human beings to establish cause-and-effect paradigms.

Determine the biologic basis for regional and cellular vulnerability of the brain during hypoglycemia with the methods noted above, as well as MRI/magnetic resonance spectroscopy along with monitoring of the infant's metabolism.

Determine long-term outcomes in neonates with asymptomatic hypoglycemia, focusing on subtle neurocognitive outcomes including executive functions.

Determine the factors that prevent brain injury from low glucose supply in exclusively breastfed infants and the potential consequences of formula feeding in such infants.

Table II

Clinical issues

General knowledge gaps
There is no evidence-based study to identify any specific plasma glucose concentration (or range of glucose values) to define pathologic “hypoglycemia.” Research studies are needed to fulfill this basic gap in knowledge and to help demonstrate the relationship between plasma glucose concentrations during the neonatal period and later neurologic outcomes.
Research agenda
Establish reliable age-based “nomograms” of postnatal plasma glucose changes in healthy term infants under varying feeding conditions during the first weeks after birth.
Establish glucose nomograms for infants with risk factors (eg, preterm, SGA, large for gestational age, IUGR; maternal history of insulin-dependent and gestational diabetes, obesity) and different diets. Such nomograms should evaluate variability with infant age and the relationship to neurodevelopmental outcomes.
Determine the effects of the frequency, severity, and duration of episodes of low plasma glucose.
Determine the effect of clinical signs (eg, seizures and coma) on neurodevelopmental outcome. Such studies should be prospective and longitudinal, as well as observational.
Determine the effects of comorbidities (eg, white matter injury, hypoxia-ischemia, sepsis) and their contribution to adverse outcomes with low plasma glucose.
Determine whether scoring systems on the basis of risk factors will generate practically useful measures of plasma glucose concentrations and alternate substrates in the neonatal period.

HIE, hypoxic ischemic encephalopathy; *IUGR*, intra-uterine growth restriction.

Table III

Laboratory tests and glucose monitoring

General knowledge gaps
There is a great inconsistency in the sources and sampling methods of blood (capillary, venous, arterial) and the methods used for subsequent analyses, including processing techniques, thus affecting establishing “normal” values on the basis of existing literature.
There are no noninvasive methods for measuring concentrations of glucose and other energy substrates (intermittently or continuously); the existing minimally invasive methods need further refinement for their utility.
The role of neuroimaging and EEG studies in the management and prediction of hypoglycemia-related neuronal injuries remains to be determined.
Research agenda
Establish biomedical and bioengineering partnerships to develop noninvasive, continuous, glucose concentration systems that are safe and accurate at all glucose concentrations encountered in newborn infants. Such equipment needs to account for the effect of local circulatory changes, edema, and shock and should not interfere with medical care of sick infants or breastfeeding of healthy infants
Development of noninvasive monitoring of alternate substrates (ketone, lactate, and pyruvate) is urgently needed.
Determine the role for neuroimaging to assess simultaneous changes in brain structure and function with plasma glucose and alternate fuel concentrations.
MRI: Establish the role of serial imaging with diffusion weighted cuts and high-resolution imaging in different layers of cortex in infants with hypoglycemia; assess the specificity of reported magnetic resonance spectroscopy lesions to hypoglycemia; establish longitudinal trends in imaging results in symptomatic cases of hypoglycemia; develop outcome prediction paradigms on the basis of neuroimaging.
Improve EEG/aEEG methods for application in hypoglycemia to help correlate the findings with simultaneous plasma glucose concentrations in the presence of comorbidities (eg, post-HIE depression, seizures, coma) and milder neurologic signs attributed to low blood glucose.

EEG, Electroencephalography.