Editor's Note: The National Institutes of Health organizes focused workshops on topics that are in need of new clinical approaches or research. This article summarizes a workshop on neonatal hypoglycemia.

—Alan H. Jobe, MD, PhD

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

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 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

GLUT	Glucose transporter
MCT	Monocarboxylate transporter
MRI	Magnetic resonance imaging
SGA	Small for gestational age

From the 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.)

Funded by NICHD and NIH Office of Rare Diseases. Additional funding was received by The March of Dimes Foundation to the general NICHD gift fund. The American Academy of Pediatrics sponsored the travels of six speakers (none is the author) to this meeting. The study sponsors and co-funders were not involved on the conference agenda, discussions of materials, and interpretation of the presentations, the writing of the report, and the decision to submit the report for publications. The opinions expressed in this article are those of the author alone. They are not necessarily those of the US Department of Health and Human Services or of the National Institutes of Health, or of the co-sponsors. The authors declare no potential conflicts.

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]