Neonatal metabolic adaptation after preterm delivery or intra-uterine growth retardation

J. M. Hawdon
Neonatal Unit, University College London Hospitals, Huntley Street, London WC1 E GAY

In utero, the fetus receives a constant supply of nutrients via the placenta. These nutrients provide energy for basal metabolism, substrates and energy for growth, and fuel stores. After birth, the neonate must adapt to an independent existence in many ways. One of the adaptive mechanisms is metabolic adaptation whereby the neonate releases fuels from body stores and utilizes substrates in milk feeds in order to meet the body’s energy needs, so that blood glucose control is achieved and alternative fuels to glucose are mobilized if necessary. The infant must adapt first to the abrupt cessation of placental nutrition and the subsequent fast-feed cycle, secondly to the change from intravenous to enteral nutrition, and third to the change of major substrate from glucose to fat.

This process, which can be likened to the adult counter-regulatory response has two main components — hormonal and metabolic. During fetal life, insulin enhances growth and the laying down of fuel stores as liver glycogen and fat in adipose tissue. After birth, the action of insulin diminishes and there is a surge in the secretion of counter-regulatory hormones — glucagon, cortisol and the catecholamines. These hormonal changes induce the enzymes responsible for the metabolic changes which release substrate from body stores: glycogenolysis, gluconeogenesis, lipolysis, and β-oxidation of fatty acids to form ketone bodies. These ketone bodies are important alternative fuels to glucose, particularly in the neonatal brain, and this contributes to total fuel availability [1,2].

Patterns of metabolic adaptation in infants

Healthy, full-term infants

First, a cross-sectional study was performed of the patterns of metabolic adaptation in 156 healthy, appropriate weight for gestational age (AGA), full-term infants [3]. Many of these babies had low pre-feed blood glucose levels although they demonstrated no clinical signs of hypoglycaemia. The same babies had high ketone body concentrations (up to 3 mmol/l), representing alternative fuel production which is thought to protect them from the neurological effects of hypoglycaemia. A close negative relationship was found between blood ketone body concentration and blood glucose on the second and third postnatal days (r, −0.57; P < 0.001). Although there was the expected positive relationship between plasma non-esterified fatty acid and blood ketone body concentrations, the relationship varied amongst full-term babies more than amongst older subjects.

Feeding patterns affected metabolism in that breast-fed infants had low blood glucose

Received 3 November 1997
concentrations but high ketone body concentrations, when compared to formula-fed infants.

**Clinically stable, preterm infants**

A similar cross-sectional study of 62 clinically stable, AGA, preterm infants demonstrated that in the absence of fluid restriction low blood glucose concentrations were rare [3]. Of greater interest is the comparison of the ketone body responses at low blood glucose levels in children, full-term neonates and preterm neonates. Whilst term infants mount a ketogenic response similar to that seen in children after an overnight fast, ketone body concentrations are low in preterm infants, even when blood glucose levels are low (maximum ketone body concentration 0.5 mmmol/l) and there is no relationship between blood ketone body and glucose concentrations [3]. It is of interest that those preterm babies who received the highest daily enteral milk feed volume had the highest ketone body concentrations after correction for birthweight, gestational age and postnatal age. This suggests that enteral feeding of preterm infants may augment postnatal metabolic adaptation.

**Intra-uterine growth retarded infants**

Infants who have undergone intra-uterine growth retardation (IUGR) are known to be at risk for hypoglycaemia. Placental insufficiency has resulted in impaired transfer of nutrients so that the fetus fails to lay down glycogen and fat stores and may even be forced to mobilize substrate from structural tissues such as muscle. This is apparent on clinical examination of the IUGR neonate. In addition, IUGR infants appear to have impaired hormonal and metabolic responses to hypoglycaemia.

In a longitudinal study of 33 IUGR babies, we demonstrated that metabolic disturbances were not confined to hypoglycaemia alone and were related to the degree and asymmetry of growth retardation [4]. At birth, the most growth-retarded preterm infants had the lowest cord blood glucose concentrations and the most growth-retarded term infants had the highest cord plasma non-esterified fatty acid concentrations, suggesting significant antenatal hypoglycaemia and stress. On the other hand, asymmetry of growth retardation was associated with high blood lactate levels in full-term infants at birth and in the immediate postnatal period. Finally, both the degree and asymmetry of growth retardation were associated with reduced availability of fatty fuels in term infants in the postnatal period (correlation of blood ketone body concentration and birthweight standard deviation score on day 3: \(r = 0.16; P = 0.011\)).

With current feeding practices which ensure adequate energy intake, the IUGR babies did not differ from their AGA counterparts in terms of the prevalence of postnatal hypoglycaemia. However, of greater clinical importance is the evidence that IUGR babies are unable to mount a ketogenic response to low blood glucose concentrations (maximum ketone body concentration 0.05 mmmol/l). Further studies of IUGR infants demonstrated that the endocrine responses to hypoglycaemia were impaired also [5].

In clinical practice it is important to determine which IUGR infants are most at risk of adverse metabolic sequelae. Our obstetric colleagues are now able to carry out comprehensive assessments of fetal well-being. One such method is the use of Doppler ultrasound to determine flow velocities in fetal blood vessels [6]. We found that IUGR fetuses with absent or negative end diastolic flow in the umbilical artery had a higher incidence of perinatal metabolic abnormalities, including hypoglycaemia and low plasma fatty acid concentrations, when compared to equally growth-retarded subjects who had normal umbilical artery Doppler waveforms. However, after the immediate postnatal period there were no metabolic differences between the two groups, perhaps related to close clinical attention and provision of adequate energy.

Finally, infants who have been exposed to perinatal hypoxia-ischaemia are at risk of failure of metabolic adaptation. Mechanisms and manifestations of metabolic disturbance vary and there is some overlap with the group of infants who have IUGR as a consequence of placental insufficiency. Asphyxiated infants are often found to be hyperlacticaemic and either hypoglycaemic or hyperglycaemic. However, plasma fatty acid and blood ketone body concentrations are low, suggesting a poor response to hypoglycaemia and reduced fuel availability.

**Conclusions**

In summary, neonatal metabolic fuel concentrations and inter-relationships are affected by a number of factors including gestational and postnatal age, intra-uterine growth retardation and perinatal stress. It is important to understand these patterns of adaptation when planning the
clinical care of infants and it is essential to use biochemical reference data taken from normal neonatal populations in future neonatal clinical and research studies.


Received 15 October 1997

---

**Impaired neonatal hepatic ketogenesis**


*Unit of Paediatric Surgery, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, University College London Medical School, 30 Guilford Street, London WC1N 1EH, U.K., and †School of Biological Sciences, University of Manchester, 2.205 Stopford Building, Oxford Road, Manchester M13 9PT, U.K.

**Why is there interest in neonatal hepatic ketogenesis?**

Hypoglycaemia characterizes the immediate post-partum period, as the newborn infant adapts to a transient period of starvation and then to the fast-feed cycle of milk feeds [1–3]. During this fetal/neonatal transition period, the onset of β-oxidation and ketogenesis provides ketone bodies (acetoacetate and β-hydroxybutyrate, derived from endogenous fat stores accumulated pre-partum) as an alternative perinatal 'energy fuel' to maternally derived glucose, the supply of which is continuous in utero, but ceases abruptly at birth [4,5]. Subsequently, throughout suckling, hepatic ketogenesis generates (from dietary triglycerides) ketone bodies which are the main circulating oxidative fuels for the brain, heart and peripheral tissues, and carbon precursors for essential myelination of the neonatal brain [6–9]. At this time, ketone bodies also have a key role as effectors that regulate: whole-body fuel selection/ utilization, neonatal glucose homoeostasis and, therefore, metabolic adaptation to extra-uterine life [3,10]. However, despite the central biochemical importance of ketogenesis to human infants, we do not currently understand precisely how it is regulated by hormones and nutrition, and controlled by enzymes and transporters, in healthy infants born at term [4,10,11]. What is clear, however, is that these profound biochemical and physiological changes that occur perinatally, including the onset of β-oxidation and ketogenesis [4], must be finely regulated and controlled to avoid infant morbidity and mortality [10].

Certain groups of clinical infants (e.g. infants who have suffered birth asphyxia; preterm or growth-retarded infants) fail to mount the ketogenic response to perinatal hypoglycaemia and, therefore, to adapt their energy metabolism appropriately to extra-uterine life [3,10,12–15]. This failure may place such infants at high risk of acute neurological dysfunction and/or longer-term severe outcomes which may be life-threatening [10,16]. Furthermore, recent evidence suggests they are predisposed to certain diseases in adult life e.g. maturity-onset diabetes [17,18]. However, until we understand precisely the ontogeny and maintenance of ketogenesis in healthy term infants, we shall not be able to understand why the mechanisms which regulate and control ketogenesis are deficient or impaired in these clinical neonates.

The aim of this paper is to report the recent quantitative research we have undertaken to ana-