During intrauterine life the growing foetus is dependent on continuous placental transfer of nutrients. Glucose is the most important foetal energy substrate. A considerable part of the transplacentally transferred glucose is used by the foetal brain. Although enzyme systems that are necessary for glucose production (gluconeogenesis) develop early, the foetus only produces its own glucose under extreme conditions, such as during maternal starvation.

In order to supply the foetus with energy, the pregnant woman increases her hepatic glucose production by 16-30 per cent. The transfer of glucose from the maternal circulation to the foetus takes place by facilitated diffusion involving glucose transporter 1, GLUT 1. The foetal blood glucose level normally corresponds to 60-80 per cent of that of the mother. Part of the transferred glucose is converted into lactate by the placenta. Lactate can be metabolized both by the mother and the foetus and is an important foetal energy substrate. Amino acids for synthesis of foetal proteins are actively transported across the placenta towards a concentration gradient. There is also a placental transfer of lipids to the foetus, but this is quantitatively less important.

During the first part of pregnancy maternal insulin sensitivity is increased, leading to formation of energy depots. Later in pregnancy, when the foetus accumulates the major part of its depot fat, the influence...
of pregnancy specific hormones and increasing insulin resistance results in mobilization of maternal energy depots. The pregnant woman almost doubles her metabolism of depot fat during the last trimester. Fatty acids formed during lipolysis contribute to the maternal energy supply, which in turn saves glucose for the foetus.

Intrauterine growth restriction is a relatively frequent problem, which may be caused by maternal, placental or foetal factors. On a global level maternal malnutrition is a dominating cause. Our group has shown that pregnant women carrying growth-retarded foetuses have a lower rate of lipolysis in the third trimester as compared to women carrying normal foetuses. As a result the pregnant woman may utilize more glucose for her own needs and consequently transfer less to the foetus.

At birth the continuous flow of energy substrates is terminated. The start of enteral feeding results in a situation characterized by a balance between lack and excess of glucose. Before the start of breastfeeding, which represents an intermittent energy supply with a high fat percentage, the newborn has to produce its own glucose, particularly for the need of the central nervous system. The brain of the newborn infant consumes much of the energy during rest, and glucose is the most important substrate for the cerebral oxidative metabolism. The hepatic glucose production in a full-term newborn infant is 4-6 mg/kg/min. This should be compared with that of an adult, which corresponds to about 2 mg/kg/min. The hepatic glucose production is proportional to the estimated brain weight both in newborn infants and children as well as in adults. Glucose is transported into the brain by facilitated diffusion, involving glucose transporters 1 and 3 (GLUT 1 and 3). These are present even in immature infants. The production of glucose is under hormonal control. During delivery, the levels of catecholamines in the neonate are increased, and there is a parallel decrease in the level of insulin and an increase in glucagon. These hormonal changes result in stimulation of glycogenolysis. In a full-term infant the depot of liver glycogen lasts only about 10 h. Consequently, glucose must also be produced by gluconeogenesis from compounds such as alanine, pyruvate, lactate and glycerol (Fig). Phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting enzyme in gluconeogenesis, is present in the foetus, but its activity increases markedly after birth, probably as a result of the decrease in the insulin/glucagon ratio. There are several reports on gluconeogenesis in newborns. Full-term newborns as well as infants with intrauterine growth restriction have been shown to be capable of converting alanine to glucose. Data from several studies also show that gluconeogenesis from glycerol takes place both in full-term and in extremely immature newborn infants. Parenteral supply of glycerol or lipids increases gluconeogenesis in extremely immature infants. It has also been shown that infants can efficiently convert lactate into glucose. Gluconeogenesis from lactate involves a recirculation of carbon atoms, which have their origin in glucose. Lactate may contribute with up to 30 per cent of the hepatic glucose production, while gluconeogenesis from alanine and glycerol contributes with 5-10 per cent each during the first day of life.

Even though a newborn infant can produce glucose at a rate corresponding to 4-6 mg/kg/min, glucose metabolism alone is not sufficient to supply the newborn with energy. Before breastfeeding has started, mobilization of depot fat is important for energy metabolism. A full-term newborn infant has depot fat corresponding to 15 per cent of the birth weight. Since the triacylglycerols of depot fat are mainly formed during the third trimester, extremely immature infants only have very limited fat stores. The depot fat in an infant born after 28 wk of gestation...
Newborn infants have a high rate of lipolysis, which corresponds to that of adults who have undergone a considerable fast. Neonatal lipolysis is stimulated by the increase in thyroid stimulating hormone (TSH) that takes places immediately after birth, probably as a result of the decrease in body temperature. The elevated levels of catecholamines are probably less important for the regulation of lipolysis during the first day of life. Hydrolysis of triacylglycerols in depot fat results in an increase in non-esterified fatty acids in the infant. Hepatic β-oxidation of fatty acids is important for the energy supply in the newborn. This process also supports gluconeogenesis by the formation of ATP and NADH. In parallel with the increase in fatty acids, there is a decrease in the respiratory quotient (RQ), indicating an increase in fat metabolism relative to that of carbohydrates. In addition to non-esterified fatty acids, lipolysis also generates glycerol, which can be converted into glucose in the gluconeogenetic process. Non-esterified fatty acids do not cross the blood-brain barrier, but ketone bodies, formed from the end product of β-oxidation, are important alternative energy substrates for the neonatal brain. Lactate can also serve as a substrate for the neonatal brain and thus decreases the need for glucose.

In addition, protein metabolism contributes to the supply of substrates for gluconeogenesis. The flow of the essential amino acid leucine has been shown to be much higher in newborns than in adults, reflecting the high neonatal protein turnover.

The blood glucose level decreases in the newborn infant during the first two hours, but then rises again to reach a steady state two to three hours after birth. Hypoglycaemia is a common neonatal problem. In most newborn infants a low blood glucose level is associated with the adaptation to extraterine life, but in the event of persistent hypoglycaemia, endocrine and metabolic disorders have to be ruled out. The definition of neonatal hypoglycaemia has been extensively discussed in the literature.

During one period neonatal hypoglycaemia was defined as a blood glucose level of <2SD in term and preterm infants. Another definition was based on the occurrence of symptoms of hypoglycaemia. This definition has been criticized, since a newborn child sometimes may have a low blood glucose level without any specific symptoms. The use of alternative substrates, such as ketone bodies and lactate, in the brain may contribute to the lack of symptoms related to hypoglycaemia in these situations. The importance of changes in sensory evoked potentials at blood glucose concentrations <2.6 mM has also been discussed. Since an adequate level of blood glucose is particularly important for the central nervous system in cases of perinatal asphyxia, special mechanisms for the maintenance of glucose homeostasis are active under this condition. Analyses of umbilical cord blood after complicated deliveries have shown low levels of insulin-like growth factor I (IGF-I) and insulin, but elevated levels of insulin-like growth factor binding protein 1 (IGFBP-1) and interleukin-6 (IL-6). These changes result in decreased peripheral glucose consumption, which in turn makes more glucose available for the infant’s central nervous system.

Studies of neonatal metabolism are often limited by the fact that only small amounts of blood or plasma are available for analysis. The use of stable isotope labelled compounds has made it technically and ethically possible to study production of energy substrates in newborn infants, both in those who are fullterm and appropriate for gestational age (AGA) and those who have a low birth weight or are born immature.

Stable isotopes of an element consist of atoms with the same number of protons in the nucleus but different numbers of neutrons. Stable isotopes are not radioactive, but owing to their differences in atomic weight compounds labelled with stable isotopes can be used as tracers in metabolic studies. H, 13C, 15N and 18O are commonly used stable isotopes. Glucose labelled with two 2H atoms has a molecular weight of 182 instead of 180 for “ordinary” glucose. Following a constant rate infusion of a compound labelled with a stable isotope and analysis of the isotope dilution by gas chromatography-mass spectrometry, the rate of appearance of the corresponding endogenous compound in the blood can be estimated. By virtue of the high sensitivity of the technique, only small amounts of the stable isotope labelled compounds need to be administered. Consequently, the kinetics of the corresponding endogenous compounds is not influenced. The technique also allows quantitation of the conversion of one compound into another, e.g., gluconeogenesis from 13C-labelled precursors of glucose. The high sensitivity and specificity of the technique make it possible to measure substrate production even in extremely immature infants and in those with a very low birth weight.
Intrauterine growth restricted infants

According to the foetal programming hypothesis, foetuses exposed to an adverse intrauterine environment may develop compensatory responses which become permanent and which may lead to later disease. Recent data on levels of glucose, insulin and IGFBP-1 support the view that in infants born small for gestational age (SGA), insulin sensitivity is reduced in the liver but increased in the periphery. Compared to AGA infants, infants with intrauterine growth restriction have smaller energy depots and higher levels of glucose precursors, which could indicate a low capacity for gluconeogenesis. However, recent data from our laboratory showed that even though rates of glucose production and lipolysis were lower in these latter infants than those found in most AGA infants, gluconeogenesis from glycerol in SGA infants was efficient. On an average, 50 per cent of the glycerol produced was converted into glucose. This conversion was higher in infants who received no extra glucose infusion, indicating that in these infants gluconeogenesis can be regulated, at least to some extent. The noted correlation between birth weight and glycerol production indicates that lipolysis is dependent on the amount of depot fat.

Preterm infants

Infants born preterm have limited substrate stores and are at risk for neonatal hypoglycaemia. The immaturity in regulation of glucose turnover in this group of infants may also result in hyperglycaemia. Our studies have shown that infants with a gestational age of 25 wk can produce glucose at a rate that corresponds to or even exceeds that of fullterm infants. In spite of their small fat depots these infants also have a capacity for lipolysis. Lipolysis can be quantitated by measuring production of glycerol by use of glycerol labelled with 2H or 13C. The rate of appearance of glycerol reflects lipolysis, since glycerol is not re-esterified in adipose tissue. Despite a marked variation between individual subjects the production of glycerol during the first day of life was not far from that found in more mature newborn infants. It has been reported earlier that the capacity for production of ketone bodies in immature infants is low, which would make these infants particularly dependent on glucose for their energy supply to the brain. It has also been postulated that immature infants have a low capacity for gluconeogenesis, but our results showed that about 30 per cent of the glycerol produced during lipolysis in extremely immature newborn infants was converted into glucose. Despite the fact that this only represents a small part of the total hepatic glucose production, the contribution may be important for avoiding hypoglycaemia. As a comparison it should be noted that fullterm infants convert 50 per cent of the produced glycerol into glucose. Further, Keshen et al. have demonstrated that immature infants can convert pyruvate into glucose.

Hofman et al. demonstrated that children born preterm had metabolic abnormalities, similar to those in children born SGA. The authors concluded that the changes occurred irrespective of whether the preterm infants were born SGA or AGA. The reduced insulin sensitivity in children born preterm may reflect an adverse postnatal environment.

Newborn infants of mothers with diabetes

Diabetic pregnancy often leads to neonatal hypoglycaemia as a result of an increase in insulin levels in the newborn infant. The increased secretion of insulin is a consequence of increased maternal blood glucose levels during pregnancy. We investigated glucose production and lipolysis in newborn infants of mothers with well controlled diabetes. The rate of glucose production was lower and the levels of insulin were higher than in normal term infants. Insulin normally inhibits lipolysis, but surprisingly the rate of lipolysis was unchanged in the infants of the diabetic mothers. An unchanged rate of lipolysis despite increased levels of insulin is probably important as a compensation for the lower rate of glucose production in these infants. A similar finding was noted in a study of an infant with familial hyperinsulinaemia.

Infants born large for gestational age (LGA)

The number of infants born LGA is increasing in many countries. It is important to study factors underlying this increase, since infants born LGA, similarly to those born SGA, are at risk both for perinatal complications and for later diseases, such as obesity, type 2 diabetes, and cardiovascular diseases. One well known problem in LGA infants is neonatal hypoglycaemia.

There is only limited information on metabolism in newborn LGA infants. The risk of neonatal hypoglycaemia and metabolic disease later in life makes it essential to study postnatal metabolic adaptation in these infants. We have investigated energy substrate production and insulin sensitivity in a group of healthy
LGA infants of non diabetic mothers. These infants were shown to have an increased rate of lipolysis, which was almost 50 per cent higher than that found in AGA infants. The increased proportion of body fat in LGA infants can be one factor explaining the high rate of lipolysis, since there was a strong correlation between rate of lipolysis and infant birth weight. The rate of glucose production in our study cohort was at the high end of the range that has been reported for AGA infants. This could reflect brain size, since the mean head circumference corresponded to +1.5 SD. The mean insulin level was higher in our infants than had been reported earlier for term AGA infants, but lower than the level found in infants of mothers with diabetes. The increased insulin levels, glucose/insulin ratios and HOMA (homeostasis model assessment) indices in the infants indicate that LGA infants have increased insulin resistance on their first day of life, similarly to older children with overweight or obesity.

Insulin is a well known inhibitor of lipolysis in adults, but this role has been questioned in the newborn. However, the results obtained in LGA infants indicate that insulin in fact has a regulatory role with regard to lipolysis in newborns, since there was a correlation between increase in insulin and decrease in lipolysis following glucagon administration.

Metabolic effects of treatment with theophylline

Medication given to the mother or the infant during or following delivery may influence the metabolism of the newborn infant. Theophylline is used in the care of immature infants with apnoea. It has both physiological and metabolic effects and could theoretically influence energy supply and intermediary metabolism in the preterm infant. Effects such as inhibition of cAMP phosphodiesterase activity and adenosine receptors could be of importance. We have investigated the effect of theophyllamine on energy substrate production in immature infants. Lipolysis of depot fat was unchanged, whereas glucose production was somewhat decreased. However, the hepatic glucose production was well within the range shown in earlier studies of newborn infants of varying gestational ages. Thus, the results showed that administration of theophylline did not result in any significant disturbances of energy substrate production in the immature newborn infant.

During intrauterine life the growing foetus depends on a continuous placental transfer of nutrients, of which glucose is the most important. Before the start of breastfeeding the newborn infant has to produce its own glucose particularly for the need of the brain. Neonatal hypoglycaemia commonly occurs in risk groups. Studies of neonatal metabolism are technically and ethically possible to perform by use of stable isotope labelled compounds both in infants born fullterm as well as in those born preterm or small for gestational age.

Acknowledgment


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