Foetal and neonatal energy metabolism in pigs and humans: a review

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ABSTRACT: The aim of this review was to elaborate a conceptual framework of the most important aspects of the main biochemical processes of synthesis and breakdown of energy substrates that human and pig foetuses and newborns can use during the transition from foetus to newborn. Under normal physiological conditions, the growth and development of the foetus depends upon nutrients such as glucose, lipids and amino acids. In addition to the maternal and foetal status, genetic factors are also reported to play a role. The main function of the placenta in all species is to promote the selective transport of nutrients and waste products between mother and foetus. This transport is facilitated by the close proximity of the maternal and foetal vascular systems in the placenta. The foetus depends on the placental supply of nutrients, which regulates energy reserves by means of glycogen storage. Also, the synthesis of foetal hepatic glycogen guarantees energy reserves during perinatal asphyxia or maternal hypoglycaemia. However, the foetus can also obtain energy from other resources, such as gluconeogenesis from the intermediary metabolism of the Krebs cycle and most amino acids. Later, when the placental glucose contribution ends during the transition to the postnatal period, the maturation of biological systems and essential metabolic adaptations for survival and growth is required. The maintenance of normoglycaemia depends on the conditions that determine nutrient status throughout life: the adequacy of glycogen stores, the maturation of the glycogenolytic and gluconeogenic pathway, and an integrated endocrine response.

Keywords: hypoxia; foetal glycogenolysis; neonatal gluconeogenesis

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1. Introduction

Research in animal (Herpin et al., 2001; Mota-Rojas et al., 2005a,b; 2006a,b) and human perinatology (Randall et al., 1979; Tollofsrud et al., 2001; Solas et al., 2004) have used sows' foetuses and newborns as experimental animal models (Gonzalez-Lozano et al., 2009a,b; Olmos-Hernandez et al., 2008), because this species has shown similarities to human medicine in terms of changes in energy metabolism during normal and pathological childbirth. Foetal growth is a complex process that involves the interaction of mother, placenta and foetus. The growth and development of the foetus depends upon nutrients such as glucose, lipids and amino acids (Trujillo-Ortega et al., 2006). At birth, the newborn has to make several adjustments to adapt to extrauterine life, such as maintaining normoglycaemia (Sperling, 1994). Before birth, foetal glucose levels are maintained by the transplacental transfer of glucose from the mother. However, there is a critical period between birth and the establishment of suckling when the newborn depends on its own hepatic glycogen stores to maintain blood glucose. Thus, the presence of appropriate hepatic glycogen stores at birth would enhance survival during this crucial transitional period. Studies of rats have shown that intrauterine growth-retarded foetuses have lower hepatic glycogen stores than normal mice (Gruppuso and Brautigan, 1989). Analyzing the products and resulting metabolites of changes in the perinatal energy metabolism will enable us to reach correct diagnoses during the perinatal period (Sanchez-Aparicio et al., 2008, 2009). However, in order to better understand such changes, it is essential to increase our knowledge of the normal metabolic processes that permit neonates to obtain energy during this period (van Dijk et al., 2006, 2008; Trujillo-Ortega et al., 2007; Orozco-Gregorio et al., 2008, 2010). The objective of this review article is to determine the main biochemical metabolic changes in the synthesis and breakdown of the energy substrates to which human and pig foetuses and newborns have access.

2. Foetal energy metabolism

Adaptation to pregnancy in humans involves major anatomic, physiological and metabolic changes in the mother that serve to support and provide for her nutritional and metabolic needs, as well as those of the growing conceptus. In this context, data from several studies in human and animal models show that glucose is the foetus' primary source of energy, while the accretion of nitrogen and protein are essential components of foetal growth and the synthesis of new foetal and maternal tissues (Kalhan, 2000). The nutrients that reach the placenta depend on the mother's intermediary metabolism and endocrine status; her partitioning of nutrients among storage, use and circulation; the capacity of her circulating transport proteins; and her cardiovascular adaptations to pregnancy, such as plasma volume expansion, which determine uterine blood flow. While all of these aspects are affected by the mother's nutritional status and infection load, the mechanisms involved are still only poorly understood. Nutritional factors are also likely to influence placental function, including vascular structure; the efficiency of placental transport systems; and the partitioning of nutrients among mother, placenta and foetus. Thus, the link between maternal nutrition and foetal nutrition is indirect; i.e., they are not the same (Fall et al., 2003). Nutrients are used by the foetus predominantly for growth and metabolism, with little energy expended on such processes as thermoregulation, movement and digestion. Foetal nutrients are in fact the main drivers of foetal growth, as genetic factors play a much smaller role. Indeed, the genetic regulation of foetal growth also seems to be regulated nutritionally, as the levels of all major hormones involved in foetal growth are regulated by circulating nutrient levels. The placenta is also a highly active organ, metabolically-speaking, with its own nutrient demands and metabolic pathways. The demands of the foetus and placenta must be in close harmony, particularly in situations where the nutrient supply is precarious, because if the placenta is starved of nutrients and fails, the foetus will be unable to survive. Therefore, in extreme cases, the placenta may even consume substrates provided by the foetus (Bloomfield and Harding, 2006). In sheep and horses, foetal glucose levels are determined primarily by the maternal nutritional state, while in pigs, they are also influenced by the relative placental mass of the foetus and the number of foetuses in the litter (Widdowson, 1971; Comline et al., 1979; Fowden et al., 1995).

2.1 Foetal growth

Foetal growth is a complex process that involves the interaction of mother, placenta and foetus. The growth and development of the foetus depends

upon nutrients such as glucose, lipids and amino acids (Trujillo-Ortega et al., 2006). In addition to the maternal and foetal status, genetic factors are also reported to play a role (Langer, 2000). In mammals, the major determinant of intrauterine growth is the placental supply of nutrients to the foetus, which occurs primarily through diffusion and transporter-mediated transport, processes that depend on the size and morphology of the placenta, its blood supply, the abundance of transporters, and its synthesis and metabolism of nutrients and hormones. Few experimental or epidemiological studies of the developmental origins of adult disease have considered the placental contribution to the resulting phenotype, and even fewer have examined the programming of the placenta per se (Sibley et al., 2005). At childbirth in humans, the placenta is an 11 m^2 exchange surface. The mother delivers oxygen and nutrients, while the foetus produces foetal waste (urea, bilirubin) and CO_2. Nutrient transport occurs through several processes. Gases, electrolytes and water, for example, pass by means of diffusion. The placenta is selectively permeable to sugar glucose, but not fructose. Amino acids, vitamins and iron (in the form of transferrin) are transported by specific receptors, but proteins (including antibodies), are transported slowly by pinocytosis. IgGs are especially important, as the foetus cannot synthesize large quantities of these agents and maternal antibodies give immunity to diseases, including smallpox, diphtheria and measles (Noden, 2002). Until the placenta develops sufficiently for hemotrophic nutrition to be established, the developing embryo must be supplied by histiotrophic nutrition. The human trophoblast is highly phagocytic, and has been shown to endocytose maternal erythrocytes and proteins. Studies have suggested that this nutrition is supplied via the uterine glands into the foetal fluid compartments. These glandular secretions contain glycogen, glycoproteins and lipids. During the first trimester, the embryo is surrounded by two fluid-filled cavities, the amniotic sac and the extraembryonic coelom. The allantoic cavity is very small in humans, compared to other species, such as the cow, pig and sheep, while the secondary yolk sac is devoid of yolk. Once placental circulation is established, the foetus receives nutrients through that organ. The placenta grows throughout gestation, but not in constant proportion to the foetus; in human pregnancy it comprises 85% of the combined foetal/placental weight at eight weeks, but only 12% at 38 weeks (Bloomfield and Harding, 2006).

In euglycemic conditions, the foetal-to-maternal glucose ratio is 70-80% in man and rabbits, 50–60% in horses, 40–50% in pigs, and 20–30% in ruminants. At term, the umbilical uptake of glucose in the foetal foal is 5–8 mg/kg/min. At birth, the neonatal liver produces glucose in the range of 4–8 mg/min (studies with lambs). In these stages, glucose utilization is closely linked to availability; i.e., the more that is available, the more that will be utilized. Indeed, the placenta's elevated metabolic activity gives it a voracious appetite for glucose. Glucose is the primary energy substrate for the foetus and is essential for normal foetal metabolism and growth. Foetal glucose metabolism is directly dependent on foetal plasma glucose concentrations. Foetal glucose utilization is augmented by the insulin produced by the developing foetal pancreas, which increases as gestation proceeds, thus enhancing glucose utilization in insulin-sensitive tissues (skeletal muscle, liver, heart, adipose tissue) that increase their mass and, hence, their demand for glucose late in gestation (Trujillo-Ortega et al., 2006; Villanueva-Garcia et al., 2006). Glucose-stimulated insulin secretion increases as gestation proceeds. Both insulin secretion and action are affected by existing glucose concentrations and the amount and activity of tissue glucose transporters. In cases of intrauterine growth restriction (IUGR), foetal weight-specific tissue glucose uptake rates and levels of glucose transporters are maintained or increased, while amino acid synthesis into protein and the corresponding insulin-like growth factor (IGF) signals a reduction in transduction proteins. These observations demonstrate the mixed phenotype of the IUGR foetus, which includes an enhanced glucose utilization capacity, but reduced protein synthesis and growth. Thus, the foetus has a considerable capacity to adapt to changes in glucose supplies by relatively common and well understood mechanisms that regulate foetal metabolism and growth, and could underlie some metabolic disorders that can appear later in life, such as insulin resistance, obesity and diabetes mellitus (Hay, 2006).

Foetal glucose metabolism depends directly on the simultaneous effects of foetal plasma glucose and insulin concentrations, which experiments in near-term foetal sheep have shown to act cumulatively to enhance foetal glucose utilization and oxidation to CO_2, according to saturation kinetics. The relative proportion of glucose oxidized during short-term, 3–4 h studies (about 55% in foetal sheep) does not change significantly over the physiological

range of foetal glucose utilization rates, indicating little or no effect of glucose or insulin on the intracellular pathways of glucose metabolism, at least in the foetus as a whole; though individual tissues and their unique cellular metabolic pathways may vary significantly in their responsiveness to glucose and insulin. Similar observations have been made for foetal metabolic rates, measured as net foetal oxygen uptake rates via the umbilical circulation, which remain relatively constant (± 5%) over the entire physiological range of oxygen supply and blood oxygen content, despite marked reductions or increases in glucose supplies (Hay et al., 1989).

Nutritional influences on foetal growth may also be mediated by nutritional regulation of foetal endocrine status. The major hormones regulating foetal growth in late gestation appear to be insulin and IGFs (Fowden, 1989; Harding et al., 1993), which regulate foetal nutrient uptake and the distribution of nutrients in the foetus. In turn, they are regulated by foetal nutrient supplies (Oliver et al., 1993, 1996). Therefore, reducing the glucose supply to the foetus decreases circulating insulin and IGF concentrations and, consequently, reduces foetal growth. Improved nutrient supplies to the foetus result in higher insulin and IGF concentrations, the redistribution of foetal nutrients, and a reduced protein breakdown, all of which foster foetal growth. In this sense, foetal growth is closely linked to nutrient supplies, a linkage that is essential if foetal demand is not to exceed the mother's capacity to supply nutrients to her concept us.

There are several other nutritional mechanisms that may allow a relative maintenance of brain growth in a substrate-limited foetus. Glucose uptake into many tissues is mediated by insulin, and foetal insulin secretion is regulated by supplies of glucose and amino acids. However, glucose uptake into the brain does not require insulin, so reduced supplies of glucose and amino acids to the foetus will decrease both circulating insulin concentrations and glucose uptake into peripheral tissues, such as muscle. The limited glucose supply available is thus reserved for uptake into tissues that do not require insulin for this process, e.g., the brain (Harding, 2001).

Though experimental data clearly show that nutrition influences foetal growth in late gestation, the mechanisms involved are not yet well understood. At first glance, it seems logical to suppose that nutrient limitation to the foetus at a given stage of development likely inhibits the growth of organs that are in a rapid growth phase at that time. However, the simple limitation of substrates to those growing organs leading to a size reduction is an inadequate explanation because, for example, maternal protein restriction in pigs results in reduced foetal weight and length at mid-gestation, a time when the foetus is still extremely small and foetal protein requirements for growth are unlikely to have functioned as a limiting factor (Pond et al., 1991).

2.2. Foetal glycogen synthesis and foetal glycogenolysis

Hepatic glycogen synthesis and storage increase during late gestation in most mammals, including man and rodents. The accumulation of glycogen stores parallels the increase in the activity of the rate-limiting enzyme for glycogen synthesis: glycogen synthase (Gruppuso and Brautigan, 1989). The foetus prepares for transition mainly in the third trimester by storing glycogen, producing catecholamines and depositing brown fat (Boxwell, 2000). In adults, insulin regulates glycogen synthesis and the activity of glycogen synthase, but in the foetus it is not clear whether insulin is the main regulator of glycogen synthesis or if other hormones, such as IGFs, play a role in this process (Frances et al., 1999). The enzymes necessary for glycogen synthesis and glycogenolysis are present in the foetal liver long before the accumulation of glycogen can be demonstrated. It is only during the last three- to four-weeks of gestation in humans that hepatic glycogen stores increase to the values at birth seen only in children with glycogen storage diseases (Darmaun et al., 1995). The endocrine events believed to trigger neonatal glucose production and the mobilization of fat from peripheral stores include increased epinephrine secretion and a rapid fall in the insulin to glucagon ratio, as occurs during the first few hours of life. This change is explained by the fall in the plasma insulin concentration and the surge in the plasma glucagon concentration that occur at that moment (Ktorza et al., 1985). As a counter-regulatory hormone for insulin, glucagon plays a critical role in maintaining glucose homeostasis *in vivo* in both animals and humans. To increase blood glucose, glucagon promotes hepatic glucose output by increasing glycogenolysis and gluconeogenesis, while decreasing glycogenesis and glycolysis in a concerted fashion via multiple mechanisms (Jiang and Zhang, 2003). In contrast, asphyxiated full-term pig

foetuses Randall (1979) showed smaller concentrations of hepatic and cardiac glycogen compared to a control group (8.6 g/100 g vs. 12.9 g/100 g humid weight and 0.24 g/100g vs. 1.29 g/100 g humid weight, respectively). However, significant differences in concentrations were not observed in muscular glycogen (8.0 vs. 8.3 g).

In chronically catheterized foetal pigs, the rates of umbilical uptake of glucose and lactate would provide a carbon supply of 5.98 g/day/kg foetal body weight, which is greater than the corresponding values calculated for the foetal lamb and foal at similar stages of gestation. The carbon requirement for oxidation and glycogen deposition in the foetal piglet during late gestation (7.22 g/day/kg foetal body weight) is also greater than that seen in the other two species when values are expressed on a weight-specific basis. While no allowances have been made for foetal uptake and losses of carbon in forms other than carbohydrates or for the carbon accumulated as new structural tissue, carbohydrates are a major source of carbon for the foetus in all three species, though the relative importance of glucose and lactate to the total carbohydrate carbon supply differs among them. Given that the lactate taken up by the umbilical circulation is probably of uteroplacental origin, the increased dependence of foetal pigs on lactate as a source of carbon may ensure that a carbon supply can be maintained to an individual foetus in a polytocous species in which littermates compete for a finite supply of maternal glucose carbon (Fowden et al., 1997).

2.3. Foetal glycolysis

During the third trimester of pregnancy, glucose uptake by the foetus has been estimated to be approximately 33 mmol/kg/min (Crenshaw, 1970). The glucose concentration in foetal circulation is close to 70–80% of that of the maternal venous plasma. This provides the foetus with a readily available energy source that enables foetal glucose consumption to reach the rates of endogenous glucose production following birth. Importantly, the enzyme systems involved in gluconeogenesis and glycogenolysis are present in the foetal liver, though they remain inactive unless stimulated by extreme maternal starvation. The foetal liver contains approximately three times more glycogen than adult livers, and at birth this storage comprises < 1% of the neonate's energy reserves. Fat oxidation is thought to be quantitatively less important than amino acid/glucose oxidation during foetal life, and rates of ketone body production are low (Hay, 1991).

2.4. Foetal gluconeogenesis

Glucose is the major energy substrate available to the placenta and foetus. It is transported across the placenta by facilitated diffusion via hexose transporters that are not dependent on insulin (Glut3 and Glut1). Although the foetus receives large amounts of intact glucose, a large quantity is also oxidized into lactate in the placenta, a product that is then used for foetal energy production. The maternal-foetal arterial glucose concentration gradient is the driving force that determines placental glucose uptake and transfer to the foetus. The glucose facilitative transporter is Glut1. It is specific for glucose and transports this substance 10 000 times faster than diffusion. However, Glut1 has a Km of 25mM for glucose, higher than maternal glucose concentrations. Glut1 expression is unaffected by hypoglycaemia, but down-regulated during hyperglycaemia. In the former condition, the foetus can perform gluconeogenesis to supply both foetal and placental tissues in the absence of maternal glucose. The placenta has specific transporters for specific fatty acids, and can obtain lipids from maternal lipoproteins. Fatty acids (FAs) are transferred by both specific transporters and simple diffusion across a maternal to foetal concentration gradient. Triglycerides do not cross the placenta, but the foetal liver can synthesize them from maternal FAs. The placenta can deliver lipids to the foetus as free FAs, but there is no strong evidence for placental assembly of lipoproteins. The foetal liver synthesizes cholesterol, but may also obtain maternal cholesterol. Maternal and foetal plasma fatty acid/lipid compositions are similar, and fatter human foetuses develop in pregnancies with high maternal plasma lipids, suggesting that foetal serum lipid concentrations depend on maternal lipid concentrations, a phenomenon apparently unique to humans (Noden, 2002). Amniotic fluid contains free amino acids that enter via transplacental and transmembranous routes from maternal sources; later, the developing foetus "ingests" these amino acids early in gestation through unkeratinized skin and, after that, through continuous swallowing of amniotic fluid (Christine et al., 2005). The foetus also needs to extract amino acids from the maternal

circulation for protein synthesis. As a result, serum levels of blood amino acids are lowered, limiting the potential for hepatic gluconeogenesis. This dilemma can be solved, at least partially, by increasing the breakdown of fat (Boden, 1996). Oxidation of these FAs generates not only energy to drive gluconeogenesis, but also the acetyl coenzyme A, which activates pyruvate carboxykinase, the first rate-limiting enzyme in the gluconeogenetic pathway (Williamsson, et al., 1966; Fanelli et al., 1993).

3. Neonatal energy metabolism

At birth, the newborn has to make several adjustments to adapt to extrauterine life, such as maintaining normoglycaemia (Sperling, 1994). Before birth, foetal glucose levels are maintained by the transplacental transfer of glucose from the mother. However, there is a critical period between birth and the establishment of suckling when the newborn depends on its own hepatic glycogen stores to maintain blood glucose. Thus, the presence of appropriate hepatic glycogen stores at birth would enhance survival during this crucial transitional period. Studies of rats have shown that intrauterine growth-retarded foetuses have lower hepatic glycogen stores than normal mice (Gruppuso and Brautigan, 1989). Glucose is an important modulator of gene expression in practically all living cells and organisms; prokaryotes as well as eukaryotes, yeasts as well as multicellular plants or animals. In vertebrates, glucose action can be either direct, when mediated by glucose itself or by glucose metabolism; or indirect, when it is secondary to glucose-dependent modifications of hormone secretion, mainly insulin and glucagon. Glucose is metabolized into pyruvate and lactate by the glycolysis Embden Meyerhof pathway. Pyruvate is metabolized to acetyl-CoA, which can enter the citric acid cycle for complete oxidation to CO_2 and H_2O, and the liberation of free energy in the form of ATP in the process of oxidative phosphorylation. Glucose also participates in other metabolic pathways: e.g., (1) conversion to its storage polymer, glycogen, by the glycogenic pathway; and, (2) the pentose phosphate pathway, a source of reducing equivalents (NADPH1) for biosynthesis, including that of FAs, and ribose, which is essential for nucleic acid synthesis (Mitanchez et al., 1997). Insulin, meanwhile, is one of the most important regulators of glucose homeostasis. It is produced specifically by pancreatic b-cells. When glucose concentrations rise, insulin is released rapidly from storage granules and the level of insulin mRNA increases through transcriptional activation and insulin mRNA stabilization. The regulation of insulin secretion at physiological glucose levels depends on the pancreatic glucose sensor system. Glucose uptake by these cells is facilitated by the high Michaelis-Menten constant of the glucose transporter Glut2. This step is not rate-limiting, and the cellular glucose concentration quickly equilibrates with changes in blood glucose concentrations. Once inside the b-cells, glucose is phosphorylated to G6-P by the specific hexokinase IV, also called GK, which exhibits a high Km for glucose (12 mm). Glucose metabolism in b-cells generates different signals that are common to many different cell types. The exact nature of the glucose-derived intermediate(s) that regulate insulin gene expression is not known, but ATP, acting on an ATP-sensitive K1 channel, is thought to play an important role in activating insulin secretion (Cook and Hales, 1984; Henquin et al., 1994). The biosynthesis and secretion of insulin by the Langerhans islets are not inevitably coupled, since these processes can be dissociated under certain conditions. Glucose-stimulated insulin release is inhibited in a calcium-free medium, whereas synthesis is still activated (Pipeleers et al., 1973a). The threshold for glucose-induced activation of insulin synthesis (2.5–3.9 mm) is lower than that for insulin secretion (4.2–5.6 mm) (Pipeleers et al., 1973b; Maldonato et al., 1977). Basal glucose utilization rates in the newborn infant are 4–6 mg/kg/min, almost twice the weight-specific rate in adults. During the first few hours of life, blood glucose concentrations fall from the foetal value, reflecting the mother's blood glucose concentration (Jezkova and Smrckova, 1990). To maintain normal levels of hepatic glucose production, the infant must have adequate stores of glycogen and gluconeogenic precursors (e.g., fatty acids, glycerol, amino acids and lactate), appropriate concentrations of the hepatic enzymes required for gluconeogenesis and glycogenolysis, and a normally functioning endocrine system. The absence of any of these requirements leads to a disruption of glucose homeostasis that usually results in neonatal hypoglycaemia (McGowan, 1999). Thermal and glycaemic stability, together with effortless respiration, are critical physiological functions that are also very closely related. Body temperature, glucose and oxygen levels are physiological variables that are controlled very precisely

by the body in health. Just as adequate oxygen and glucose levels are essential to cellular metabolism, the appropriate body temperature is critical to the functioning of the enzymatic systems that regulate cellular functions (Thomas, 1994).

3.1. Neonatal glycogenolysis

With the loss of the continuous infusion of glucose through the placenta, the plasma glucose concentration in the healthy term newborn falls during the first two hours after birth, reaching a nadir no lower than 40 mg/dl, before stabilizing by 4–6 h of age in the range of 45–80 mg/dl. Glucose concentrations are maintained immediately after birth by the breakdown of hepatic glycogen (glycogenolysis) in response to epinephrine and glucagon, facilitated by falling insulin levels. In the full-term human foetus, the concentration of hepatic glycogen is 80–180 mg/g of tissue; a concentration that is higher than at any other stage of life (Adam, 1971). In piglets, the reserves of corporal glycogen are between 30–38 g/kg b.w. (Okai et al., 1978); however, glycogen is depleted during the first 8–12 h, after which glucose levels are maintained by the synthesis of glucose from lactate, glycerol and alanine (gluconeogenesis). As feeding is established and carbohydrate intake becomes adequate, gluconeogenesis is no longer required (Srinivasan et al., 1986). After cord clamping, the neonate's blood glucose concentration falls, reaching its lowest point at 1–2 h. At this point, hepatic glycogen stores are depleted and gluconeogenesis replaces glycogenolysis, such that while the glucose concentration is low, the brain does not become fuel deficient. The endocrine events believed to trigger neonatal glucose production and the mobilization of fat from peripheral stores include increased epinephrine secretion and a rapid fall in the insulin to glucagon ratio, as occurs during the first few hours of life. This change is accounted for by both a fall in the plasma insulin concentration and a surge in the plasma glucagon concentration that occur at this time (Ktorza et al., 1985). The neonate defends itself against hypoglycaemia by decreasing insulin production and simultaneously increasing secretions of glucagon, epinephrine, growth hormone and cortisol, hormones that work together in a counter-regulatory function that counteracts the effect of insulin and thus causes increased hepatic glucose output by other means, initially from insulin and decreased glucagon (Sunehag and Haymond, 2002). When insulin is given in increasing amounts, in hyperinsulinemic-euglycemic clamps, there is a rapid increase in glucose storage and glucose oxidation, both exhibiting saturation kinetics, but the latter reaches a plateau at insulin levels < 20% of that required to saturate storage. The partition between oxidation and storage is probably variable and depends, among other factors, on muscle sensitivity to insulin relative to other tissues. This is supported by observations of transgenic mice with tissue-selective deletion of the insulin receptor: mice with skeletal muscle deletion of insulin receptor oxidize less glucose and store more as fat (Bruning et al., 1998; Kim et al., 2000).

3.2. Neonatal gluconeogenesis

In animal foetuses, the activity of one or more important rate-limiting enzymes of gluconeogenesis (pyruvate carboxylase, phosphoenol/pyruvate carboxykinase, glucose-6-phosphatase, or fructose 1,6 diphosphatase) is absent or very low, does not increase until the perinatal period, and reaches adult levels only after several hours, or days, of extrauterine life (Darmaun et al., 1995).

In the newborn, serum glucose levels decline after birth until the age of 1–3 h, when they spontaneously increase. Liver glycogen stores become rapidly depleted within hours of birth, and gluconeogenesis, primarily from alanine, can account for 10% of glucose turnover in the newborn infant by several hours of age (Halamek et al., 1997).

The gluconeogenic pathway utilizes those glycolytic reactions that are reversible, plus four additional reactions that circumvent the irreversible non-equilibrium reactions. The enzymes that catalyze these non-equilibrium reactions are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase, and glucose 6-phosphatase (G6P), glucose 6-phosphate dehydrogenase, L-type pyruvate kinase, phosphofructokinase-1, fructose 6-phosphate 2-kinase/fructose 2,6-bisphosphatase and glucokinase (GK) (Mitanchez et al., 1997).

Most of the body's tissues can utilize monosaccharides, FAs and/or amino acids as precursors for energy generation. Under normal conditions, four tissues are absolutely dependent upon glucose for energy metabolism; i.e., they cannot utilize fatty acids or amino acids. The four glucose-dependent tissues are nervous tissue, adrenal medulla, red

blood cells and testes. One of the functions of the liver is to maintain normal blood glucose levels so that these tissues always have an adequate supply of glucose for energy generation. To achieve this, the liver stores glucose as the polysaccharide glycogen when this substance is plentiful. When it becomes scarce, the liver breaks down (hydrolyzes) glycogen and releases glucose into the blood. The liver also synthesizes glucose from precursors that contain three or four carbon atoms, and this newly synthesized glucose is then available to maintain blood glucose levels. The kidney also has the ability to store glucose as glycogen, to release glucose from glycogen, and to synthesize glucose (Villanueva-Garcia et al., 2006; Olmos-Hernandez et al., 2010). During starvation, the kidneys' ability to synthesize glucose is stimulated and frees the liver to perform other necessary functions. Skeletal muscle can store glucose as glycogen, break down glycogen for its own use, and has a very limited capacity to synthesize glucose from three and four carbon precursors. Skeletal muscle performs these biochemical processes in order to insure adequate glucose concentrations for contraction. It is from the Krebs cycle that the pathways for glucose, lactose, fatty acid, glycerol and non-essential amino acid synthesis evolve. The synthesis of these latter must, of course, be balanced to ensure the optimal functioning of the cell, the organs and the animal itself. More importantly, these processes must be balanced against the requirement to generate energy by the Krebs cycle.

Based on physiological situations that entail increased energy expenditures, such as exercise, gestation, and lactation, and on the general concept of the existence of an adipostat or energy stat, increased energy expenditure in humans or other mammals should not necessarily lead to weight loss (just as a low metabolic rate does not necessarily lead to obesity) (Golozoubova et al., 2004). However, this theoretical opinion is countered by experimental observations showing that chronic treatment of animals with agonists does indeed lead to weight loss (Ghorbani et al., 1997).

4. Conclusions

The aim of this review was to elaborate a conceptual framework of the most important aspects of the main biochemical processes of synthesis and breakdown of energy substrates that human and pig foetuses and newborns can use during the transition from foetus to newborn. This is a critical time period, as it entails processes of physiological change for the human or animal newborn that begin *in utero* when the foetus prepares for the transition from intrauterine placental support to extrauterine self-maintenance. Much has been written about the energy metabolism during the perinatal period in humans and animals. The importance of studies with pig-based animal models for human medicine is due to the similarities in the modifications of energy metabolism implemented in these two species during the processes of normal and pathological childbirth. Advances in research leading to improved knowledge of the metabolic processes, thermal and glycaemic stability and effortless respiration, show that these are all critical physiological functions identified in animal research that contribute to a better understanding of pathologies with etiologies in different, varied physio-metabolic alterations. Thus, these studies increase the possibility of survival through early mother-foetal assessments and adequate pharmacologic treatments. The link between maternal and foetal nutrition is indirect, i.e., they are not the same thing. At birth, the newborn must switch abruptly from a state of net glucose uptake and glycogen synthesis to one of independent glucose production and homeostasis. The maintenance of normoglycaemia depends on the conditions that determine nutrient status throughout life: the adequacy of glycogen stores, the maturation of the glycogenolytic and gluconeogenic pathway, and an integrated endocrine response. In and of themselves, neonatal hypoglycaemia, hypothermia and hypoxia are not pathological conditions but, rather, symptoms of illness or of a failure to adapt from the foetal state of continuous transplacental glucose, warmth and oxygen consumption to the extrauterine environment and pattern of intermittent nutrient supply, all of which are variables closely interrelated to the successful transition from uterine to extrauterine life in animals and humans and, ultimately, to their survival.

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