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Role of placental insufficiency and intrauterine growth restriction on the activation of fetal hepatic glucose production

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ABSTRACT

Glucose is the major fuel for fetal oxidative metabolism. A positive maternal–fetal glucose gradient drives glucose across the placenta and is sufficient to meet the demands of the fetus, eliminating the need for endogenous hepatic glucose production (HGP). However, fetuses with intrauterine growth restriction (IUGR) from pregnancies complicated by placental insufficiency have an early activation of HGP. Furthermore, this activated HGP is resistant to suppression by insulin. Here, we present the data demonstrating the activation of HGP in animal models, mostly fetal sheep, and human pregnancies with IUGR. We also discuss potential mechanisms and pathways that may produce and support HGP and hepatic insulin resistance in IUGR fetuses.

1. Early activation of hepatic glucose production in IUGR fetus

1.1. Normal fetal glucose metabolism

Glucose is the primary fuel for fetal oxidative metabolism (Hay, 2006; Hay et al., 1983). It is delivered to the fetus by facilitated diffusion across the placenta according to its maternal–fetal concentration gradient (Hay et al., 1990), eliminating the need for endogenous hepatic glucose production (HGP) by the fetus (Hay et al., 1984). Indeed, studies using catheters across the liver in normal fetal sheep have shown that there is net hepatic glucose uptake, rather than hepatic glucose output (Houin et al., 2015; Teng et al., 2002a,b; Timmerman et al., 2000). The absence of fetal hepatic glucose output is advantageous for the fetus as it helps maintain the maternal–fetal glucose concentration gradient and transfer of maternally derived glucose to the fetus (Thureen et al., 1992).

1.2. Development and regulation of hepatic glucose production after birth

The induction of hepatic gluconeogenesis normally occurs at birth (Fowden et al., 1998; Girard, 1990). Gluconeogenesis is regulated such that expression of phosphoenolpyruvate carboxykinase (*PCK1, PCK2*), glucose-6-phosphatase (*G6PC*), and fructose-1,6-bisphosphatase (*FBP1*) are normally quiescent until just prior to birth when increases in glucagon, cortisol, and catecholamines activate the glycogenolytic and gluconeogenic pathways (Fowden et al., 1998; Hanson and Reshef, 1997; Pilkis and Granner, 1992). Insulin is the dominant mechanism for suppressing gluconeogenic gene expression and glucose production in the adult (Edgerton et al., 2009; Ramnanan et al., 2010). The inability of insulin to suppress HGP and uncontrolled HGP are hallmarks of type 2 diabetes.

1.3. Increased hepatic glucose production in the IUGR fetus

Intrauterine growth restriction (IUGR) is a significant cause of increased fetal and neonatal mortality and morbidity, affecting 6–10% of all pregnancies and up to 30% of those ending in preterm delivery (Brar and Rutherford, 1988; Pollack and Divon, 1992; Tuuli et al., 2011). IUGR also increases the risk of preterm birth and development of diabetes and obesity during the lifespan (Martin-Gronert and Ozanne, 2007; Symonds et al., 2009; Thorn et al.,

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2011).

In animal models of IUGR, early developmental shifts in fetal glucose metabolism include decreased pancreatic insulin secretion, increased hepatic gluconeogenic gene expression, and increased HGP (Limesand et al., 2007, 2006; Nijland et al., 2010; Park et al., 2008; Thorn et al., 2009, 2011). Specifically, fetal sheep with placental insufficiency-induced IUGR demonstrate increased HGP rates and hepatic gluconeogenic gene expression at 90% of a full term gestation (*PCK1, PCK2, G6PC*) (Gentili et al., 2009; Limesand et al., 2007; Thorn et al., 2013, 2009). Increased HGP, hepatic gluconeogenic gene expression, and growth restriction are also present in fetal sheep exposed to chronic hypoglycemia (>8wk) produced by maternal insulin infusion and subsequent maternal hypoglycemia (Carver and Hay, 1995; Thorn et al., 2012). Further, increased expression of *PCK1* is found in the nutrient restricted fetal baboon liver (Nijland et al., 2010) and in the IUGR neonatal rodent liver (Lane et al., 2002).

An early activation of gluconeogenic gene expression has also been observed in animal models of maternal over nutrition or high fat diet exposure in mice, rats, sheep, and non-human primates (McCurdy et al., 2009; Plata Mdel et al., 2014; Rattanatray et al., 2014; Strakovsky et al., 2011; Zhou et al., 2015). The mechanisms for the activation of gluconeogenic genes during intrauterine exposures to increased or decreased nutrients remain unclear. Interestingly, in the non-human primate model of maternal high fat diet exposure, mothers who have a more severe metabolic phenotype, characterized by increased obesity and insulin resistance, also have reduced placental blood flow, increased placental cytokines, and produce offspring at 1 year of age with persistent hepatic steatosis and inflammation (Frias et al., 2011; Thorn et al., 2014). This raises the possibility that placental insufficiency and an associated signal or nutrient deficiency may be a commonality between these different maternal exposures.

There are no known studies in human IUGR pregnancies that directly test for human fetal HGP, though there are studies in neonates that support dysregulated HGP. Human newborn infants who were small for gestational age (SGA), pre-term, or pre-term and very low birth weight (VLBW) demonstrate impaired glucose and insulin suppression of HGP (Chacko et al., 2011; Cowett et al., 1983; Goldman and Hirata, 1980; Kalhan et al., 1986). Kalhan et al. found a 20% higher basal rate of HGP in SGA infants which was suppressed by only ~50% during glucose infusion (Kalhan et al., 1986). Chacko et al. also found that VLBW infants had sustained HGP during periods of both high glucose infusion (and high insulin concentrations) and low glucose infusion (and low insulin concentrations) (Chacko et al., 2011). Thus IUGR neonates demonstrate persistently increased HGP that is not reduced in the presence of increased glucose and insulin concentrations.

2. Mechanisms for the early activation of fetal HGP in the IUGR fetus

2.1. Reduced fetal nutrient supply

Reduced nutrient supply is an important component of IUGR, as noted in all animal models of glucose or protein restriction including rodents, baboons, and sheep, as well as in humans (Martin-Gronert and Ozanne, 2007; Nijland et al., 2010; Rozance et al., 2006; Thorn et al., 2012). The IUGR fetus produced by placental insufficiency receives lower supplies of not only glucose and amino acids, but also oxygen, from the placenta (Brown et al., 2012; Thorn et al., 2013). The role that each of these nutrient restrictions has, in addition to other hormonal and substrate regulatory pathways, in the activation of HGP and insulin resistance in the IUGR fetus is discussed below.

2.2. Fetal hypoglycemia

Experimental models in pregnant sheep of reduced fetal glucose supply, producing physiologic hypoglycemia, include acute hypoglycemia induced by maternal fasting for several days (Fowden and Forhead, 2012; Hay et al., 1984) or prolonged maternal insulin infusions (DiGiacomo and Hay, 1989; 1990; Hay et al., 1990; Rozance et al., 2008; Thorn et al., 2012). These models can be used to determine the specific effect of fetal hypoglycemia versus other characteristics that are also present in IUGR fetuses produced by placental insufficiency (Table 1). Prolonged exposure to hypoglycemia (>2 wk) is sufficient to reduce fetal growth. These models also produce fetal hypoglycemia and hypoinsulinemia, similar to IUGR, but independent of generalized placental insufficiency and other pathophysiologic hallmarks of marked IUGR, notably uteroplacental ischemia, fetal hypoxemia, and increased fetal lactate concentrations (Carver and Hay, 1995; DiGiacomo and Hay, 1989; 1990; Rozance et al., 2008). Similar to the IUGR fetus, the hypoglycemic fetus increases fetal HGP and hepatic gluconeogenic gene activation (DiGiacomo and Hay, 1989; 1990; Fowden and Forhead, 2012; Hay et al., 1981; Narkewicz et al., 1993; Rozance et al., 2008; Thorn et al., 2012). Acute hypoglycemia can also activate HGP, as HGP has been directly measured using hepatic catheterization as evidenced by net hepatic glucose output, rather than uptake, following hypoglycemia for 4 d (Houin et al., 2015).

2.3. Fetal hypoinsulinemia

Insulin is the primary hormone responsible for suppressing gluconeogenic gene expression and glucose production (Edgerton et al., 2006; Pilkis and Granner, 1992). Fetal hypoglycemia results in decreased fetal insulin secretion (DiGiacomo and Hay, 1990; Rozance et al., 2006, 2007), and fetal hypoinsulinemia is found in IUGR fetuses and in hypoglycemic models with increased HGP (Table 1) (DiGiacomo and Hay, 1990; Thorn et al., 2012). Whether hypoinsulinemia alone is sufficient for the induction of glucose production remains unclear, as pancreatectomized fetuses fail to induce glucose production (Fowden and Forhead, 2012; Fowden and Hay, 1988), yet streptozotocin-treated fetuses have increased glucose production (Hay et al., 1989). Differences between these models may reflect differences in counter-regulatory hormone responses, as glucagon production is prevented by pancreatectomy but is not affected by streptozotocin (Fowden and Forhead, 2012; Hay et al., 1989). Furthermore, the independent or synergistic effects of hypoinsulinemia and increased counter-regulatory hormones (see section 2.6) on the regulation of fetal HGP are often hard to determine, due to their frequent co-existence when HGP is active.

Table 1
Comparison of IUGR produced by placental insufficiency and hypoglycemic fetal sheep.

Fetal characteristics	IUGR (placental insufficiency)	Hypoglycemia
Growth restriction	Yes	Yes
↓ Glucose	Yes	Yes
↓ Insulin	Yes	Yes
↑ Lactate	Yes	No
↓ Oxygen	Yes	No
Hepatic metabolism		
Glucose production	Yes	Yes
Insulin resistance	Yes	No
Increased glycolysis	Yes	No
Decreased glucose oxidation	Yes	No