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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.

Keywords

fetus; IUGR; glucose; liver; insulin resistance

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., 2002, 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).

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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 (*FBPI*) 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., 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, Limesand et al., 2006, Nijland et al., 2010, Park et al., 2008, Thorn et al., 2009, Thorn et al., 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, Thorn et al., 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, Rattanatrav 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, DiGiacomo and Hay, 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, DiGiacomo and Hay, 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, DiGiacomo and Hay, 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, Rozance et al., 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.

2.4 Hepatic insulin sensitivity during IUGR

Recent data demonstrate differences in the capacity for acute hyperinsulinemia to suppress HGP between fetal sheep models of hypoglycemia (HG) and IUGR. Specifically, during a high dose acute hyperinsulinemic clamp, the IUGR fetus maintained an increased rate of glucose production while glucose production was suppressed in the HG fetus made chronically hypoglycemic with 3 wks of restricted glucose supply from the mother (DiGiacomo and Hay, 1989, DiGiacomo and Hay, 1990, Thorn et al., 2013). Further, a physiological increase in insulin concentrations for 1 wk in the chronically (~8 wk) exposed HG fetus demonstrated maintained hepatic insulin action on suppression of genes regulating hepatic gluconeogenesis (*PCK1*, *G6PC*, *FBP1*, glucose transporter 2: *GLUT2*, and the transcriptional co-activator *PGC1A*) (Thorn et al., 2012). This finding is important because IUGR from placental insufficiency develops over at least this long a gestational period and the IUGR fetus develops resistance to the ability of insulin to suppress fetal HGP. One of the major differences between the HG and IUGR models is fetal oxygenation status. Oxygenation is normal in the HG fetus, in contrast to the IUGR fetal sheep, which has a ~50% reduction in fetal arterial blood oxygen content and pO_2 and increased lactate concentrations (Aldoretta et al., 1994, Carver and Hay, 1995, Thorn et al., 2013, Thorn et al., 2012). Despite these differences, both HG and IUGR fetuses have similar oxygen consumption rates (Carver and Hay, 1995, Narkewicz et al., 1993, Thorn et al., 2009, Thureen et al., 1992). Thus, hypoglycemia alone may be sufficient to induce HGP, but lower oxygen values may have an additional effect on glucose production and insulin sensitivity in the IUGR fetus (Table 1).

2.5 Fetal hypoxia

Chronic hypoxemia, as occurs in IUGR fetuses, has been induced in fetal sheep and effects measured on blood flow, the cardiovascular system, and endocrine function (Imamura et al., 2004, Kitahara et al., 1989, Myers et al., 2005, Myers et al., 2014). Effects of chronic

hypoxia on the fetal liver has been less studied. Acute hypoxia results in the activation of HGP, although this may represent glycogenolysis rather than gluconeogenesis (Apatu and Barnes, 1991, Fowden et al., 1998, Stratford and Hooper, 1997, Teng et al., 2002). The effect of chronic hypoxia on fetal HGP and hepatic insulin action has not been tested to our knowledge. Human pregnancies at high altitude are a natural experimental model to study chronic hypoxia and IUGR. These studies have focused on placenta function and nutrient delivery and found decreased glucose transport and delivery to the fetus (Illsley et al., 2010, Skeffington et al., 2015, Zamudio et al., 2010), similar to the reduced glucose uptake found in the IUGR sheep fetus (Limesand et al., 2007, Thureen et al., 1992).

2.6 Increased counter-regulatory hormones

Cortisol and glucagon are important activators of fetal HGP during late gestation (Fowden et al., 1998, Pilkis and Granner, 1992). Indeed, premature elevations in fetal cortisol and a lower insulin:glucagon ratio have been found after chronic fetal hypoglycemia (2–8wk) and in placental insufficiency IUGR models, in parallel with increased fetal HGP (Rozance et al., 2008, Thorn et al., 2013). Fetal dexamethasone infusion also increases hepatic activity of PEPCK (encoded by *PCK1*) and G6Pase (encoded by *G6PC*) in rodents and sheep, but does not induce hepatic glucose output when measured in sheep (Franko et al., 2007, Nyirenda et al., 1998, Timmerman et al., 2000). In addition to directly activated HGP and gluconeogenic gene expression, elevated cortisol concentrations have been proposed to precede increases in catecholamine concentrations (Fowden et al., 1998), which could further potentiate glucose production. Indeed, adrenalectomized fetal sheep demonstrate a blunted response to the activation of glucose production in response to maternal fasting (Fowden and Forhead, 2011). Adrenal demedulated fetal sheep also have reduced catecholamine secretion in response to hypoxia (Yates et al., 2012), supporting an inverse relationship between fetal oxygenation and catecholamine concentrations which may drive HGP in the IUGR fetus (Limesand et al., 2007). Lastly, experimental fetal glucagon administration in fetal sheep induces endogenous hepatic glucose output and decreases glutamate output (Devaskar et al., 1984, Philipps et al., 1983, Teng et al., 2002).

2.7 Molecular and signaling pathways

The mechanisms responsible for increased HGP and the inability of insulin to suppress HGP in the IUGR fetus may include the combined effects of endocrine cues and associated changes in hormone and nutrient signaling pathways. The IUGR fetal liver has increased expression of *PGC1A* mRNA, nuclear hepatic nuclear factor (HNF4 α), and phosphorylation of cAMP regulated binding protein (CREB) supporting the potential role of cAMP-dependent signaling in mediating HGP (Limesand et al., 2007, Nyirenda et al., 2006, Rhee et al., 2003, Thorn et al., 2009). AMPK activated protein kinase (AMPK) is a key nutrient sensor of decreased energy state and activation of AMPK (phosphorylation) decreases HGP in rodents (Shaw et al., 2005, Zhou et al., 2001). Interestingly, the IUGR fetal sheep liver has a lack of activation of nutrient and cell stress proteins, like AMPK or eIF2 α , (Thorn et al., 2009), despite hypoxia and low energy status. This suggests that the IUGR sheep fetus may have an adaptive strategy for survival during placental insufficiency that would include reduced nutrient sensing and reduced insulin sensitivity that may contribute to increased HGP. In contrast, rat models of IUGR produced by uterine artery ligation, and guinea pig

models with hypoxia during gestation produce offspring with hepatic oxidative stress and intrauterine treatment with Exendin-4 or N-acetylcysteine improves the liver metabolic phenotype in both of these models (Hashimoto et al., 2012, Raab et al., 2009). The mechanisms underlying the differences between these models may relate to the timing or severity of exposure to the intrauterine insult.

Components in the proximal insulin pathway are similar between CON and IUGR fetal livers; even in IUGR fetuses, insulin robustly activates nuclear AKT protein (Thorn et al., 2013, Thorn et al., 2009). This suggests discordance between normal proximal insulin signaling to AKT and failure of insulin to suppress gluconeogenic gene expression and HGP in the IUGR fetus (Figure 1). Improper forkhead box protein O1 (FOXO1) activation and regulation may contribute to increased HPG and gluconeogenic gene expression (Thorn et al., 2013). Basal phosphorylation of FOXO1 is higher in the IUGR liver and is not increased further with insulin nor is nuclear localization reduced, despite normal AKT activation (Thorn et al., 2013). FOXO1 activity is regulated by post-translational modifications (PTMs) (Calnan and Brunet, 2008). Recent data suggest that cell stress and hypoxia cause specific PTMs that prevent FOXO1 nuclear exclusion. Nuclear phosphorylation of c-Jun N-terminal kinase (JNK) also is increased in the IUGR liver with insulin (Thorn et al., 2013). JNK activation has been shown to prevent nuclear export and degradation of FOXO1 (Greer and Brunet, 2008). Thus increased JNK activation in IUGR may antagonize AKT-induced phosphorylation, which has classically been viewed as the inactivation signal for FOXO1 nuclear exclusion (Figure 1).

2.8 Epigenetic regulation

Placental insufficiency and intrauterine exposures to decreased nutrient supply may result in altered epigenetic regulation of metabolic genes. Indeed, decreased DNA methylation at the *PCK1* promoter has been observed in the fetal baboon liver from nutrient restricted mothers (Nijland et al., 2010). The effect of placental insufficiency on epigenetic regulation of fetal gluconeogenesis has not been studied. Epigenetic regulation of gluconeogenic genes and transgenerational inheritance has been observed in models of maternal high fat diet exposure and in embryo-transferred IUGR rat offspring (Strakovsky et al., 2011, Thamocharan et al., 2007).

3. Hepatic substrate metabolism and coordinated changes that may support HGP in the IUGR fetus

3.1 Normal fetal hepatic substrate and oxygen metabolism

Studies using direct hepatic catheterization have shown that the normal fetal sheep liver has a net uptake of glucose, lactate, and most amino acids that exceeds its rate of oxidative metabolism and anabolic activity, with a simultaneous release of glutamate, pyruvate, and, to a lesser amount, serine, aspartate, and ornithine (Cetin et al., 1992, Teng et al., 2002, Timmerman et al., 2000). The fetal liver also consumes ~21% of total fetal oxygen consumption under normal basal conditions, supporting its high metabolic rate (Holcomb and Wilkening, 1999, Houin et al., 2015, Rudolph, 1983). To our knowledge, no studies have measured the hepatic uptake of oxygen or carbon substrates during IUGR when HGP

occurs. Here, we discuss changes in fetal substrate concentrations, net fetal uptake of substrates, and liver-related metabolic data in the IUGR fetus that provide insight into the metabolic changes that result in HGP.

3.2 Lactate

The IUGR fetus has higher lactate concentrations and increased hepatic lactate dehydrogenase (*LDH*)A gene expression, raising the possibility that lactate might drive HGP (Brown et al., 2015, Thorn et al., 2013, Thorn et al., 2009). *LDHA* encodes the M protein subunit of the LDH enzyme and favors lactate and NAD⁺ formation in liver (Draoui and Feron, 2011). Given the absence of a decrease in *LDHB* expression and assumption that there is sufficient LDH activity, the IUGR fetal liver would be able to convert lactate back to pyruvate for use in the gluconeogenic pathway (Brown et al., 2015).

3.3 Amino Acids

The liver plays an important role in the metabolism of amino acids. In the adult, the liver is responsible for the metabolism of ~90% of the dietary amino acids that are disposed (Brosnan, 2000, Jungas et al., 1992). Amino acids are also important carbon substrates for HGP and can increase HGP (Brosnan, 2000, Krebs et al., 2003). It is unknown, however, if amino acids are used as a gluconeogenic substrate when HGP is active, as in the IUGR fetus. Recent data suggest that in response to acute fetal hypoglycemia, there is increased hepatic uptake of amino acids and coordinated changes in the shuttling of intrahepatic amino acids that likely provide carbon substrates for HGP (Houin et al., 2015). In the IUGR fetus the pathways for hepatic amino acid metabolism have not been studied. Interestingly, prolonged infusion of amino acids (~12d) in normal late gestation fetal sheep did not significantly increase gluconeogenic gene expression, although fetal plasma glucagon concentrations were increased, raising the potential for indirect priming of the glucogenic pathway (Maliszewski et al., 2012).

3.4 Glycogen, glycerol, and free fatty acids

The increase in HGP in the IUGR fetus is likely due to gluconeogenesis rather than glycogenolysis, as liver glycogen content is similar between CON, HG, and IUGR fetuses (Limesand et al., 2007, Rozance et al., 2008, Thorn et al., 2013, Thorn et al., 2009, Thorn et al., 2012). Based on this data, glycogenolysis cannot be the sole source of HGP and endogenous gluconeogenic pathways are likely activated. Other substrates, including glycerol and free fatty acids (FFA) fuel HGP postnatally. However, in the fetus, lipids provide little fuel for oxidative metabolism and net glycerol uptake by the fetus under normal conditions is quantitatively small (0.6 $\mu\text{mol}/\text{min}/\text{kg}$) (Teng et al., 2002). Thus, the role of glycerol and FFA in fueling HGP in the fetus are unlikely.

3.6 Integration and coordination of hepatic metabolism during IUGR

Overall, coordinated changes in hepatic metabolism are needed to support the energy and carbon requirements for HGP in the IUGR fetus. Specifically, gluconeogenesis requires two 3-carbon molecules and energy substrates (4 ATP and 2 GTP). Recent data provide insight into these metabolic adaptations in the IUGR liver and fetus (Figure 2). First, although the

IUGR fetal sheep has severe reductions in blood O_2 content and pO_2 (Thorn et al., 2013) it adapts to maintain glucose utilization rates, and has lower glucose oxidation and increased lactate production (Brown et al., 2015, Limesand et al., 2007). There is also increased hepatic expression of phosphofructokinase 1 (*PFK1*), *LDHA*, and pyruvate dehydrogenase kinase 4 (*PDK4*) mRNA in the IUGR liver (Brown et al., 2015). Thus, increased hepatic *LDHA* expression and lactate production, as a result of increased glycolysis (*PFK1*) and incomplete glucose oxidation (*PDK4*), may provide lactate as a carbon source for HGP in the IUGR fetus. Second, the suppression of glucose oxidation, via *PDK4*, may spare substrates such as pyruvate, lactate, and alanine from oxidative metabolism and allow these carbon substrates to be used as gluconeogenic precursors (Herbst et al., 2014, Tao et al., 2013). Increased pyruvate carboxylase (*PC*) then favors the conversion of pyruvate into oxaloacetate (OAA) (Brown et al., 2015). Third, increased HGP (Thorn et al., 2013) and gluconeogenic gene expression occurs simultaneously with increased glycolysis (*PFK1*) creating a potential futile cycle in glucose metabolism in the IUGR fetal liver. In terms of energetics, the increase in *LDHA* and lactate production would be predicted to produce a concomitant increase in NAD^+ , which is necessary to sustain a high glycolytic flux. A high glycolytic flux rate may occur to generate ATP needed for gluconeogenesis or to compensate for lower ATP production as a result of decreased glucose-derived pyruvate oxidation. Fourth, there is increased gene expression of both the cytosolic (*PCK1*) and mitochondrial (*PCK2*) forms of PEPCK enzyme in the IUGR fetal liver (Brown et al., 2015, Thorn et al., 2013). Emerging data in rodents and isolated cells indicate that both of these forms of PEPCK are important for HGP and that each form may have unique roles in coordinating substrate preference and mitochondrial metabolism (Mendez-Lucas et al., 2013, Mendez-Lucas et al., 2014, She et al., 2000, Stark et al., 2014, Stark and Kibbey, 2014, Yang et al., 2009). Lastly, FOXO1 may provide a molecular link between these metabolic pathways, specifically increased *PCK1* and *PDK4* (as shown in Figure 1).

4. Consequences of increased HGP in offspring who were IUGR

The early activation of HGP in utero may be an important adaptive response to supply glucose for other glucose-consuming fetal tissues (Thorn et al., 2011). In the adult, the liver is the major organ responsible for glucose production (Cherrington, 1999, Moore et al., 2012) and uncontrolled hepatic HGP is a major contributor to T2DM (Samuel et al., 2009, Samuel and Shulman, 2012, Sun and Lazar, 2013). Thus persistently increased or dysregulated HGP after birth in offspring who were IUGR will increase the risk for T2DM in later life (Martin-Gronert and Ozanne, 2007, Symonds et al., 2009, Thorn et al., 2011, Vuguin et al., 2004). Other coordinated changes in hepatic metabolic pathways also contribute to metabolic disease risk. Studies in rodent models of fetal hypoxia and IUGR support a progressive decrease in hepatic mitochondrial function that worsens across the lifespan and ultimately results in impaired oxidative phosphorylation, lipid accumulation, insulin resistance, and diabetes (Al-Hasan et al., 2013, Cao et al., 2012, Lane et al., 1996, Lane et al., 2001, Lane et al., 2002, Magee et al., 2008, Peterside et al., 2003, Rueda-Clausen et al., 2011, Simmons et al., 2001, Vuguin et al., 2004). Studies in humans support these findings in animal models and demonstrate that adults who were IUGR are at increased risk for development of increased hepatic HGP and NAFLD (Alisi et al., 2011,

Nobili et al., 2008) in addition to diabetes and obesity (Gluckman et al., 2009, Hales and Barker, 2001, McMillen and Robinson, 2005). Therefore, identification of the mechanisms for HGP in utero during IUGR is critical to allow for the successful design and implementation of future targeted therapeutic strategies to reverse hepatic insulin resistance in IUGR infants following delivery, decrease persistent hepatic HGP, increase mitochondrial oxidation, and, potentially, reduce later life risk for T2DM and associated metabolic diseases.

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Highlights

- Intrauterine growth restricted fetuses have increased hepatic glucose production.
- Mechanisms include changes in hormone signals, insulin action, and substrate supply.
- Increased hepatic glucose production is a complication in IUGR neonates.
- Persistence across the life span is a hallmark of type 2 diabetes.

Figure 1. Potential role of FOXO1 on metabolic pathways in the IUGR fetal liver

The IUGR fetal liver has increased nuclear FOXO1. (A) We speculate that hypoxia may induce nuclear P-FOXO1 accumulation via HIF and/or JNK signaling at sites which prevent (B) insulin mediated FOXO1 inactivation via AKT and nuclear exclusion. This leads to insulin resistance and increased hepatic glucose production (*PCK1*), decreased glucose oxidation (*PDK4*), increased glycolysis (*PFK1*), and increased lactate production (*LDHA*).

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