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Prenatal Programming of Insulin Secretion in Intrauterine Growth Restriction

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Abstract

Intrauterine growth restriction (IUGR) impairs insulin secretion in humans and in animal models of IUGR. Several underlying mechanisms have been implicated, including decreased expression of molecular regulators of β-cell mass and function, in some cases shown to be due to epigenetic changes initiated by an adverse fetal environment. Alterations in cell cycle progression contribute to loss of β-cell mass, whereas decreased islet vascularity and mitochondrial dysfunction impair β-cell function in IUGR rodents. Animal models of IUGR sharing similar insulin secretion outcomes as the IUGR human are allowing underlying mechanisms to be identified. This review will focus on models of uteroplacental in sufficiency.

Keywords

intrauterine growth restriction; β-cells; diabetes; insulin secretion

Intrauterine Growth Restriction (IUGR) and Diabetes in Humans

Impaired fetal growth increases the risk of later diabetes and impaired glucose tolerance, even after correction for gestational age, current body size, and socioeconomic status.[1–4] Poor growth before birth can account for ≥18% of diabetes prevalence in currently ageing populations,[5] with associated infant catch-up growth adding further to diabetes risk.[6,7] Some of this association between birth weight and diabetes may reflect the effect of genetic polymorphisms which reduce insulin action in fetal life as a growth promoter as well as after birth. For example, mutations in the glucokinase gene that impair pancreatic glucose sensing and cause maturity onset diabetes of the young also reduce birth weight when inherited by the fetus,[8] probably because these individuals secrete less insulin before birth leading to reduced fetal and placental growth.[9] Conversely, genes which predispose the mother to type 2 diabetes mellitus (T2DM) and gestational diabetes may increase fetal growth and cause

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T2DM in progeny who inherit the maternal copy, as shown for the T2DM-predisposing allele of the *TCF7L2* gene.[10] These genotypes may contribute to the "U"-shaped relationship seen between birth weight and diabetes risk in some, but not all, studies.[1–3] Intriguingly, effects of fetal growth on diabetes risk may also be modulated by genotype.[11] For example, polymorphisms of peroxisome proliferator-activated receptor-γ 2, which regulates development and metabolic function of adipose tissue, increase the risk of developing T2DM only if subjects were born small for gestational age.[12]

Low birth weight is consistently associated with impaired insulin sensitivity in children and adults,[1] although this is preceded by enhanced insulin sensitivity in neonates during catch-up growth.[13,14] However, impaired insulin sensitivity does not by itself cause diabetes. T2DM develops only when insulin secretion and its determinants, β-cell function and mass, and their capacity to increase (plasticity), are inadequate to compensate for insulin resistance.[15] It is now clear that defects in insulin secretion are common in the general population, and can precede insulin resistance and determine if T2DM develops.[16] This review therefore focuses on effects of restricted fetal growth on insulin secretion.

IUGR and Insulin Secretion in Humans

Glucose-stimulated insulin secretion and glucose removal are impaired in the severely IUGR human fetus.[17] This may in part reflect decreased β-cell mass, which was reduced in a study of severely IUGR fetuses (<1.5 kg).[18] Although Béringue et al[19] did not find altered β-cell mass in less severely restricted human fetuses (<10th percentile for birth weight), this might also reflect the variety of causes of IUGR and range of gestational ages within their cohort. In humans, although effects of IUGR on postnatal β-cell mass have not been reported, measures of basal and glucose-stimulated insulin secretion are not consistently related to birth weight.[1] In some studies, a positive relationship between birth weight and insulin secretion may reflect compensatory increases in insulin secretion in response to developing insulin resistance, whereas in others a negative relationship may reflect late stages of β-cell failure.[1]

However, insulin secretion *relative to insulin sensitivity and hence demand* is substantially impaired in children and adults who grow poorly before birth in most,[13,20,21] although not all studies,[22] and occurs before onset of insulin resistance. Young men of low birth weight had a 30% lower insulin secretion than appropriate for their insulin sensitivity,[20] that is, a reduced insulin disposition index. Critically, insulin secretion is deficient in adult humans who were IUGR and is the first defect in glucose homeostasis that they exhibit.[20] Thus, poor growth before birth reduces insulin secretion relative to that needed to maintain insulin action at a given level of insulin resistance, suggesting that the plasticity of insulin secretion and its underlying determinants are impaired following IUGR in humans.

Restricted Fetal Growth and Insulin Secretion in Other Animal Species

Animal models have a normal genetic background upon which environmental effects during gestation or early postnatal life can be tested for their role in inducing an abnormal metabolic phenotype. The most commonly used animal models of IUGR are caloric or protein restriction, induction of uteroplacental insufficiency, or glucocorticoid

administration in the pregnant rodent, sheep, guinea pig, and non-human primate. Remarkably, results from many of these investigations seem to suggest a common offspring phenotype of impaired β-cell function consistent with observations in IUGR humans.

Ovine Studies

Placental Restriction (PR)—Studies in the sheep have allowed direct investigation of effects of restricted placental growth and function, and hence restricted fetal growth, on glucose metabolism, insulin action and their determinants throughout prenatal and postnatal development. We have extensively characterized the effects of surgical restriction of placental growth and function (PR) in sheep, induced by removal of most endometrial placental implantation sites before mating.[23] This limits placental delivery of substrates including oxygen and glucose to the PR fetus, which exhibits the endocrine adaptations and reduced growth also characteristic of human IUGR, including reduced circulating and tissue levels of insulin-like growth factor-I (IGF-I) and other anabolic hormones and an early and amplified prenatal surge of cortisol.[24] PR can also be induced in sheep by sustained maternal hyperthermia throughout months 2 to 4 of the 5-month pregnancy[25–29] or by maternal overnutrition throughout adolescent pregnancy,[30] with similar consequences for impaired placental and fetal growth, fetal glucose, amino acid and oxygen supply, and fetal metabolism. These experimental paradigms in sheep also allow direct fetal in vivo studies, because of its relatively large size and tolerance of catheterization in utero. Prenatal consequences of PR for insulin secretion and disposition have been well characterized in the hyperthermia model of PR[31–34] and in our studies of surgically induced PR. Only insulin sensitivity, and not insulin secretion, has been reported to date in the overnourished adolescent model. Postnatal consequences of PR for insulin secretion in the sheep have to date been reported in surgically induced PR and after PR due to maternal overnutrition in adolescent pregnancy.

Before birth, the surgically induced PR sheep fetus has reduced insulin secretion in vivo, although this is normal when corrected for insulin sensitivity.[35] Similarly, the more severe IUGR induced by hyperthermia in sheep (58% reduction in fetal weight cf. 25% in surgical PR) reduces basal and glucose-stimulated insulin secretion in absolute terms, although secretion relative to insulin sensitivity has not been reported.[31,33] β-cell mass and proliferation are decreased in the hyperthermia-induced PR sheep fetus at 0.7 gestation, and low oxygen and glucose together with elevated catecholamines are implicated as causal.[36] These hyperthermia-induced IUGR fetuses are more insulin-sensitive than controls, which may partially compensate for decreased secretion to maintain insulin action.[33]

By 1 month of age, the IUGR lamb has lost the enhanced maximal insulin disposition seen before birth,[37,38] suggesting that increased insulin demand, with excess nutrient intake in the neonatal period associated with catch-up growth,[39] has induced emerging defects in β-cell function and its plasticity. This progresses to major deficits in basal and stimulated insulin secretion relative to insulin sensitivity in the young adult, particularly males.[40] Similarly, inducing PR by overfeeding adolescent pregnant sheep increases fasting glucose concentrations and impairs glucose tolerance in 6-month-old adolescent progeny, without increases in fasting plasma insulin concentration or glucose-stimulated insulin secretion,[41]

also suggesting failure of compensatory insulin secretion in this model. As young adults, 12-month-old IUGR progeny in this nutritional PR model still had elevated fasting glucose but not impaired glucose tolerance, although the adult studies had limited power with only 3 to 6 progeny per sex and treatment combination.[41] We look forward to results of studies in progeny from heat-stressed ewes and comparison of the long-term effects of these paradigms of IUGR in the sheep.

Rodent Studies

In industrialized countries, uteroplacental insufficiency is the most common cause of IUGR. We have developed a model of restricted blood flow to the fetus by bilateral uterine artery ligation in the pregnant rat at day 18 or 19 of gestation.[42,43] At birth, IUGR newborns have decreased weight, normal mass and numbers of β-cells, and β-cell function is markedly impaired, seen as blunted first phase insulin secretion. Glucose-stimulated and leucine-stimulated insulin release from isolated islets is markedly impaired, but arginine-stimulated insulin release is normal, suggesting that the secretory apparatus is intact.[42,43] As the animals age, β-cell mass in IUGR progeny progressively declines, falling to ∼10% of control values by 6 to 9 months of age.[42,44]

Mechanisms of Impaired Insulin Secretion after IUGR

Ovine Studies

Fetal Life—Normal insulin secretion relative to insulin sensitivity in the surgically induced PR sheep fetus reflects normal basal and enhanced maximal β-cell function in vivo[35] combined with reduced absolute but not relative β-cell mass.[38] Enhanced fractional insulin secretion by isolated islets in response to glucose is seen in the heat stress–induced model of PR, but total insulin secretion is still impaired, because of reduced pancreatic insulin content and expression and lower glucose oxidation.[31,32] In this more severe model of IUGR, β-cell mass was only 24% that of control fetuses, with a similar reduction in β-cell mitotic rate.[31]

Postnatal Life—By 1 month of age, in our studies of surgically induced PR and control animals, the IUGR lamb has lost the enhanced maximal (glucose-stimulated) β-cell function seen before birth,[37,38] with a reversal of the birth weight and β-cell relationship. Although *basal* β-cell function was still enhanced in the IUGR lamb, *maximal* β-cell function was substantially impaired in terms of insulin disposition per gram β-cell mass.[38] This suggests that within a month after birth, and worsening with age, PR and IUGR offspring are unable to respond adequately to the increased demand for insulin postnatally, because of β-cell functional deficits and impaired plasticity after birth. We also found that pancreatic expression of the L-type voltage-gated Ca channel (α1D) was reduced, and furthermore, that its expression was highly predictive of maximal insulin secretory function in the young male lamb.[38] This represents an early onset and newly uncovered molecular defect in β-cell function in PR and IUGR that is revealed upon the postnatal challenge of increased blood glucose and hyperphagia. Small size at birth was also associated with decreased expression of the Kir6.2 unit of the K_{ATP} channel in female lambs.[38] Mutations in this gene predict either hyperinsulinism of infancy or diabetes in humans, depending on effects of the particular mutation on function, suggesting this as an additional novel molecular mechanism

for impaired insulin secretion after IUGR. These data demonstrate that pancreatic expression of key determinants of insulin secretion are reduced in young PR offspring, and that expression cannot be upregulated to maintain insulin action after birth. In contrast to their impaired function, β-cell mass is normal following neonatal catch-up growth in 1 month old PR and IUGR lambs, indicating that it is has been able to expand in response to increased postnatal nutrient supply.[38] The further expansion of relative β-cell mass before adulthood in PR sheep is preceded by increased pancreatic gene expression of *Pdx1, Igf2*, and the insulin receptor, and the latter 2 correlate positively with β-cell volume density, mass and islet density, consistent with activation of these key regulatory pathways in β-cell mass plasticity.[38]

Negative effects of IUGR on insulin action progress further with ageing such that major deficits in basal and glucose-stimulated β-cell function underlie impaired insulin disposition in the young adult sheep.[38,40] Although β-cell mass is increased in the young IUGR adult male sheep,[38,40] this is insufficient to maintain insulin disposition and glucose tolerance, suggesting that IUGR impairs the plasticity of β-cell mass.

Rodent Studies

Regulation of β-Cell Mass—Intriguingly, offspring of multiple rodent models of IUGR display marked reductions in β-cell mass, indicating that the β-cell plays a primary role in the development of the metabolic phenotype. Several transcription factors are essential for the development of the endocrine and exocrine pancreas.[45] The embryonic development of β-cells is critically dependent on the function of the basic helix-loop-helix transcription factor neurogenin 3 (Ngn3). Pdx1 (also known as IDX1, IPF1, STF1, XlhBox8, GSF, and IUF) is a homeodomain-containing transcription factor that plays 2 critical roles, first in the early development of both endocrine and exocrine pancreas, and then in the later differentiation of the β-cell. Targeted homozygous disruption of *Pdx1* in mice results in pancreatic agenesis, and homozygous mutations yield a similar phenotype in humans.[45]

During embryonic development, fewer Ngn3-positive (− 20%) and Pdx1-positive (− 47%) cells are present in the pancreas of calorically restricted or PR fetuses compared with controls, indicating that nutrient restriction decreases the β-cell precursor pool.[44,46] The loss of Pdx1 expression persists into adulthood contributing to the progressive decline in β-cell mass after PR.[44] The molecular mechanisms underlying this loss of Pdx1 expression are secondary to epigenetic modifications at its proximal promoter region.[47] Similar epigenetic modifications at *Pdx1* have been observed in islets from humans with T2DM.[48]

Islet Vascularity—In our previous studies, IUGR in the rat markedly reduced islet vessel density, which preceded the reduction in β-cell mass by several weeks.[49] This temporal relationship suggests that islet vascularization directly determines β-cell mass, a paradigm supported by the ability of vascular endothelium to regulate β-cell proliferation through direct interaction with integrins on the surface of β-cells.[50] In IUGR rats, vascular endothelial growth factor (VEGF) expression was reduced after birth, as was subsequent vascular density measured at 2 weeks. Surprisingly, we observed a return to normal *VEGF* mRNA levels by postnatal day 7 and normal protein expression by postnatal day 14 in IUGR

rats. The discordance between *VEGF* mRNA and protein levels at postnatal day 7 led us to postulate that IUGR caused differential expression of the various splice isoforms of *VEGF*, as different isoforms produce varying degrees of local angiogenic stimulus with varying degrees of retention in the surrounding extracellular matrix.[51] However, we did not observe any major shifts in the balance of *VEGF* isoform expression in IUGR. Another possibility is that IUGR induces expression of inhibitory *VEGF* splice variants, the $VEGF_{XXXb}$ family of isoforms.[52] Finally, it is possible that IUGR induces a downregulation of *VEGF* receptors, such as flk-1 and flt-1; however, we found no effects of IUGR on their expression.[49] Thus, the precise mechanisms underlying the observed reduction in islet vascularity in IUGR islets remain to be determined.

Mitochondrial Dysfunction—Multiple studies have now shown that IUGR is associated with increased oxidative stress in the human fetus.[47] In particular, low levels of oxygen, evident in IUGR fetuses, decrease the activity of complexes of the electron transport chain, which will generate increased levels of reactive oxygen species (ROS).[47] Overproduction of ROS leads to oxidative damage not only in the mitochondria but also in cellular proteins, lipids, and nucleic acids. β-cells are especially vulnerable to attacks by ROS because expression of antioxidant enzymes in pancreatic islets is very low,[53] and β-cells have a high oxidative energy requirement. Increased ROS impair glucose-stimulated insulin secretion,[54–56] decrease expression of key β-cell genes[57] and induce cell death.[58] Increased ROS levels inactivate the iron-sulfur centers of the electron transport chain complexes and tricarboxylic acid cycle aconitase, resulting in shutdown of mitochondrial energy production.

A key adaptation enabling the fetus to survive in a limited energy environment may be the reprogramming of mitochondrial function.[47] However, these alterations in mitochondrial function can have deleterious effects, especially in cells that have a high energy requirement, such as the β-cell. The β-cell depends upon the normal production of ATP for nutrient-induced insulin secretion[59] and proliferation,[55] so that an interruption of mitochondrial function can have profound consequences for β-cell function.

We have found that uteroplacental insufficiency induces oxidative stress and marked mitochondrial dysfunction in the fetal rat β-cell,[43] resulting in impaired insulin secretion. The activities of complexes I and III of the electron transport chain progressively decline in IUGR islets, impairing ATP production which deteriorates further with age. Mitochondrial DNA point mutations accumulate with age and are associated with decreased mtDNA content and reduced expression of mitochondrial-encoded genes in IUGR islets. Thus, IUGR induces mitochondrial dysfunction in the fetal β-cell leading to increased production of ROS, which in turn damage mtDNA.[43] A self-reinforcing cycle of progressive deterioration in mitochondrial function leads to a corresponding decline in β-cell function. Finally, a threshold in mitochondrial dysfunction and ROS production is reached and diabetes ensues. These studies suggest that a major mechanism by which IUGR in the rodent impairs insulin secretion is impaired mitochondrial function in the β-cell. Although reduced β-cell mass contributes to insulin secretory defects in the IUGR rat, studies that have controlled for β-cell mass[42,44] demonstrate that IUGR also induces an insulin secretory defect.

Summary

IUGR impairs insulin secretion in humans and in animal models of IUGR, consistently reflecting impaired β-cell function. IUGR may also decrease β-cell mass, although initial compensatory increases are seen in some models. Several underlying mechanisms for loss of β-cell mass and function have been implicated in animal models, including decreased expression of molecular regulators of β-cell mass and function, shown in some cases to be due to epigenetic changes initiated by an adverse fetal environment. Alterations in cell cycle progression, with increased apoptosis and loss of neogenesis, contribute to loss of β-cell mass, whereas decreased islet vascularity and mitochondrial dysfunction impair β-cell function in IUGR rodents. Animal models of IUGR that share similar insulin secretion outcomes as the IUGR human are allowing underlying mechanisms to be identified. This is now progressing to evaluation of intervention strategies aimed at improving insulin secretion and reducing the risk of diabetes in humans whose growth was restricted before birth.

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