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Developmental Origins of Diabetes: The Role of Oxidative Stress

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Abstract

The 'thrifty phenotype' hypothesis proposes that the fetus adapts to an adverse intrauterine milieu by optimizing the use of a reduced nutrient supply to ensure survival, but by favoring the development of certain organs over that of others, this leads to persistent alterations in the growth and function of developing tissues. This concept has been somewhat controversial, however recent epidemiological, clinical, and animal studies provide support for the developmental origins of disease hypothesis. Underlying mechanisms include reprogramming of the hypothalamic-pituitary-adrenal axis, islet development, and insulin signaling pathways. Emerging data suggests that oxidative stress and mitochondrial dysfunction may also play a critical role in the pathogenesis of type 2 diabetes in individuals who were growth retarded at birth.

Keywords

intrauterine growth retardation; type 2 diabetes; Barker hypothesis; fetal origins of adult disease

Introduction

It is becoming increasingly apparent that the in utero environment in which a fetus grows and develops may have long-term effects on subsequent health and survival (1, 2). The landmark cohort study of 300,000 men by Ravelli and colleagues showed that exposure to the Dutch famine of 1944–45 during the first half of pregnancy resulted in significantly higher obesity rates at age 19 (3). Subsequent studies demonstrated a relationship between low birth weight and the later development of cardiovascular disease (4) and impaired glucose tolerance (5–7) in men in England. Those men who were smallest at birth (2.5 kg) were nearly seven times more likely to have impaired glucose tolerance or type 2 diabetes than were those who were heaviest at birth. In addition, the investigators found a similar relationship between lower birth weight and higher systolic blood pressure and triglyceride levels (8). Subsequent studies in diverse populations through the world have demonstrated a significant correlation between low birth weight and the later development of type 2 diabetes (9–18). More recent studies controlling for the confounding factors of socioeconomic status and lifestyle factors have further strengthened the association with low birth weight and increased risk of coronary heart disease, stroke, and type 2 diabetes (11, 18). In 1976 the Nurses' Health Study was initiated and a large cohort of U.S. women born from 1921 to 1946 was established. The associations with low birth weight and increased risk of coronary

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heart disease, stroke, and type 2 diabetes remain strong even after adjusting for lifestyle factors such as smoking, physical activity, occupation, income, dietary habits, and childhood socio-economic status and occur independently of the current level of obesity or exercise (18). In a study of 22,000 American men, those born lighter than 5.5 lb had a significantly higher incidence of adult hypertension and type 2 diabetes compared with average birth weight adults (11). Similar to the Nurses Health Study, the association between birth weight and later disease is largely independent of the lifestyle risk factors (11).

Recent observations have shown that impaired growth in infancy and rapid childhood weight gain exacerbate the effects of impaired prenatal growth. The highest risk for the development of type 2 diabetes is among adults who were born small and become overweight during childhood (17, 19–21).

The mechanisms underlying the association between size at birth and impaired glucose tolerance or type 2 diabetes are unclear. A number of studies in children and adults have shown that non or pre-diabetic subjects with low birth weight are insulin resistant and thus predisposed to development of type 2 diabetes (9, 12–15, 20–27). Intrauterine growth retardation (IUGR) is known to alter the fetal development of adipose tissue, which is closely linked to the development of insulin resistance (15, 28, 29). Other studies have shown that the adverse effect of intrauterine growth retardation on glucose homeostasis was mediated through programming of the fetal endocrine pancreas (1, 30, 31). Jensen and colleagues (31) measured insulin secretion and insulin sensitivity in a well-matched Caucasian population of 19-year-old glucose tolerant men with birth weights of either below the 10th percentile (small for gestational age-SGA) or between the 50th-75th percentile (controls). To eliminate the major confounders such as "diabetes genes", none of the participants had a family history of diabetes, hypertension, or ischemic heart disease. There was no difference between the groups with regard to current weight, body mass index (BMI), body composition, and lipid profile. When controlled for insulin sensitivity, insulin secretion was reduced by 30%. However insulin sensitivity was normal in the SGA subjects. The investigators hypothesized that defects in insulin secretion may precede defects in insulin action and that once SGA individuals accumulate body fat, they will develop insulin resistance (31).

What Animal Models Can Tell Us

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 diabetes. For a comprehensive survey of the numerous animal models of fetal growth retardation, the reader is referred to two excellent reviews (32,33). The most commonly used animal models are caloric or protein restriction, glucocorticoid administration, or induction of uteroplacental insufficiency in the pregnant rodent. In the rat, maternal dietary protein restriction (approximately 40–50% of normal intake) throughout gestation and lactation has been reported to alter glucose homeostasis and hypertension in the adult offspring (34–39). Offspring are significantly growth retarded, remain growth retarded throughout life, and in some cases develop mild ß-cell secretory abnormalities (34–38) and in others insulin resistance (36,39). Aged rats develop hyperglycemia characterized by defects in insulin signaling in muscle, adipocytes, and liver (39–43).

Fetal overexposure to glucocorticoids either via maternal administration or by inhibition of placental 11beta-hydroxysteroid Dehydrogenase Type 2 (11ßHSD2) in the rat induces hypertension, glucose intolerance and abnormalities in hypothalamic-pituitary-adrenal (HPA) function after birth (44–47).

To extend these experimental studies of growth retardation, we developed a model of uteroplacental insufficiency (IUGR) induced by bilateral uterine artery ligation at day 18 of gestation (term is 22 days) in the rat that restricts fetal growth (48,49). Growth retarded fetal rats have critical features of a metabolic profile characteristic of growth retarded human fetuses: decreased levels of glucose, insulin, insulin-like-growth factor 1 (IGF-I), amino acids, and oxygen (50–52). By 6 months of age, IUGR rats develop diabetes with a phenotype remarkably similar to that observed in the human with type 2 diabetes: progressive dysfunction in insulin secretion and insulin action. Thus, the studies in various animal models support the hypothesis that an abnormal intrauterine milieu can induce permanent changes in glucose homeostasis after birth and lead to type 2 diabetes in adulthood.

Cellular Mechanisms: Mitochondrial dysfunction and oxidative stress

The intrauterine environment influences development of the fetus by modifying gene expression in both pluripotential cells or terminally differentiated, poorly replicating cells. The long-range effects on the offspring (into adulthood) depend upon the cells undergoing differentiation, proliferation, and/or functional maturation at the time of the disturbance in maternal fuel economy. The fetus also adapts to an inadequate supply of substrates (such as glucose, amino acids, fatty acids, and oxygen) by metabolic changes, redistribution of blood flow, and changes in the production of fetal and placental hormones which control growth.

The fetus' immediate metabolic response to placental insufficiency is catabolism: it consumes its own substrates to provide energy. A more prolonged reduction in availability of substrates leads to a slowing in growth. This enhances the fetus' ability to survive by reducing the use of substrates and lowering the metabolic rate. Slowing of growth in late gestation leads to disproportion in organ size, since organs and tissues that are growing rapidly at the time are affected the most.

Uteroplacental insufficiency, caused by such disorders as preeclampsia, maternal smoking and abnormalities of uteroplacental development, is one of the most common cause of fetal growth retardation. The resultant abnormal intrauterine milieu restricts the supply of crucial nutrients to the fetus thereby limiting fetal growth. Multiple studies have now shown that intrauterine growth retardation is associated with increased oxidative stress in the human fetus (53–59). A major consequence of limited nutrient availability is an alteration in the redox state in susceptible fetal tissues leading to oxidative stress. In particular, low levels of oxygen, evident in growth-retarded fetuses, will decrease the activity of complexes of the electron transport chain, which will generate increased levels of reactive oxygen species (ROS) (60–62). Overproduction of ROS initiates many oxidative reactions that lead to oxidative damage not only in the mitochondria but also in cellular proteins, lipids, and nucleic acids. 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 (62–64). However, these alterations in mitochondrial function can have deleterious effects, especially in cells that have a high energy requirement, such as the ß-cell. The ß-cell depends upon the normal production of ATP for nutrient-induced insulin secretion (65–72) and proliferation (73). Thus, an interruption of mitochondrial function can have profound consequences for the ß-cell.

Mitochondrial dysfunction can also lead to increased production of reactive oxygen species (ROS), which will lead to oxidative stress if the defense mechanisms of the cell are overwhelmed. ß-cells are especially vulnerable to attacks by ROS because expression of

antioxidant enzymes in pancreatic islets is very low (74,75), and ß-cells have a high oxidative energy requirement. Increased ROS impair glucose stimulated insulin secretion (73,76,77), decrease gene expression of key ß-cell genes (78–84), and induce cell death (85–87).

We have found that uteroplacental insufficiency induces oxidative stress and marked mitochondrial dysfunction in the fetal ß-cell (88). ATP production is impaired and continues to deteriorate with age. The activities of complexes I and III of the electron transport chain progressively decline in IUGR islets.

Mitochondrial DNA point mutations accumulate with age and are associated with decreased mtDNA content and reduced expression of mitochondrial-encoded genes in IUGR islets. Mitochondrial dysfunction results in impaired insulin secretion. These results demonstrate that IUGR induces mitochondrial dysfunction in the fetal ß-cell leading to increased production of ROS, which in turn damage mtDNA (88). A self-reinforcing cycle of progressive deterioration in mitochondrial function leads to a corresponding decline in ß-cell function. Finally, a threshold in mitochondrial dysfunction and ROS production is reached and diabetes ensues.

Mitochondrial dysfunction is not limited to the ß-cell in the IUGR animal. IUGR animals exhibit marked insulin resistance early in life (prior to the onset of hyperglycemia), characterized by blunted whole body glucose disposal in response to insulin and impaired insulin suppression of hepatic glucose output (89). Basal hepatic glucose production is also increased (89). Oxidation rates of pyruvate, glutamate, succinate, and α-ketoglutarate are significantly blunted in isolated hepatic mitochondria from IUGR pups (prior to the onset of diabetes) (63). Rotenone-sensitive NADH-O_2 oxidoreductase activity is similar in control and IUGR mitochondria, showing that the defect responsible for decreased pyruvate, glutamate and α̃ ketoglutarate oxidation in IUGR liver precedes the electron transport chain and involves pyruvate and α-ketoglutarate dehydrogenases. Increased levels of manganese superoxide dismutase (MnSOD) suggest that an antioxidant response has been mounted and 4-hydroxynonenal (HNE) modification of pyruvate dehydrogenase E2 catalytic and E3 binding protein subunits suggests that HNE-induced inactivation of this key enzyme may play a role in the mechanism of injury. These results indicate that uteroplacental insufficiency impairs mitochondrial oxidative phosphorylation in the liver and this derangement predisposes the IUGR rat to increased hepatic glucose production by suppressing pyruvate oxidation and increasing gluconeogenesis (63).

Mitochondria in muscle of IUGR young adult rats, prior to the onset of hyperglycemia, exhibit significantly decreased rates of state 3 oxygen consumption with pyruvate, glutamate, α-ketoglutarate and succinate (64). Decreased pyruvate oxidation in IUGR mitochondria is associated with decreased ATP production, decreased pyruvate dehydrogenase activity and increased expression of pyruvate dehydrogenase kinase 4 (PDK4). Such a defect in IUGR mitochondria leads to a chronic reduction in the supply of ATP available from oxidative phosphorylation. Impaired ATP synthesis in muscle compromises energy-dependent GLUT4 recruitment to the cell surface, glucose transport and glycogen synthesis, which contributes to insulin resistance and hyperglycemia of type 2 diabetes (64).

Other animal models of fetal growth retardation also show mitochondrial abnormalities. Mitochondrial DNA content is reduced in liver, pancreas and skeletal muscle of male offspring of dams fed a low-protein diet during pregnancy and lactation (90,91). This was associated with reduced expression of mitochondrial DNA-encoded genes (91).

A number of recent studies in humans further suggest that mitochondrial dysfunction may contribute to type 2 diabetes. Studies using ^{13}C and ^{31}P magnetic resonance spectroscopy (MRS) have shown decreases in mitochondrial activity and increases in intramyocellular fat content in young insulin-resistant offspring of parents with type 2 diabetes, a group that has a strong tendency to develop diabetes later in life (92). Expression of genes involved in oxidative phosphorylation is reduced among patients with type 2 diabetes mellitus and insulin resistance (93), although this may be an effect rather than a cause of diabetes.

Conclusions

The combined epidemiological, clinical, and animal studies clearly demonstrate that the intrauterine environment influences both growth and development of the fetus and the subsequent development of adult diseases. There are critical specific windows during development, often coincident with periods of rapid cell division, during which a stimulus or insult may have long-lasting consequences on tissue or organ function postnatally. Birthweight is only one marker of an adverse fetal environment and confining studies to this population only may lead to erroneous conclusions regarding etiology. Studies using animal models of uteroplacental insufficiency suggest that mitochondrial dysfunction and oxidative stress play an important role in the pathogenesis of the fetal origins of adult disease.

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Practice Points

- Uteroplacental insufficiency, caused by such disorders as preeclampsia, maternal smoking and abnormalities of uteroplacental development, is one of the most common cause of fetal growth retardation.
- Intrauterine growth retardation is linked to the later development of type 2 diabetes.
- A key adaptation enabling the fetus to survive in a limited energy environment may be the reprogramming of mitochondrial function
- An abnormal intrauterine milieu leads to the development of mitochondrial dysfunction which in turn impairs function of key cells such as the ß-cell.

Research Agenda

- The effect of antioxidants on the long-term complications of intrauterine growth retardation should be investigated.
- The underlying molecular mechanisms linking oxidative stress and the development of diabetes in individuals who were growth retarded at birth needs to be further elucidated.
- Nutritional strategies optimizing postnatal growth of IUGR babies needs further evaluation.

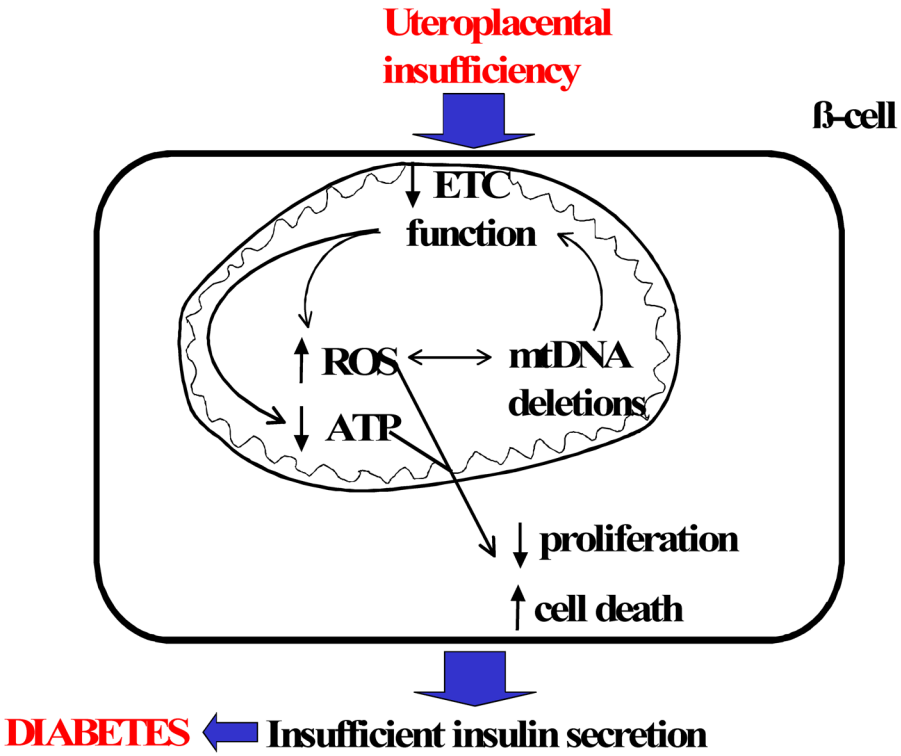

Figure 1.
Decreased nutrients and oxygen availability to the fetus result in mitochondrial dysfunction which in turn results in increased production of reactive oxygen species (ROS) and decreased production of ATP. Mitochondrial dysfunction in key cells such as the beta-cell in the pancreas decreases cell proliferation and increases cell death culminating in the development of type 2 diabetes.