Early Growth and Development of Later Life Metabolic Disorders

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Abstract
Growth is effected via a complex interaction of genetic, nutritional, environmental and growth factors. Hormonal factors such as the growth hormone (GH) and insulin-like growth factor (IGF) signaling system, the human placental lactogen, and insulin play an integral role in early growth. Genetic factors affecting the GH-IGF system and insulin secretion and actions, and epigenetic mechanisms including DNA methylation have been further implicated as contributory factors. These hormonal systems, on a background of genetic susceptibility, together with other factors including maternal nutrition, placental and environmental factors, regulate not only early growth but also development. These interactions may impact on later health consequences in adult life. Accumulating data in the last few decades on developmental programming and later life metabolic disorders has provided a novel perspective on the possible pathogenesis of metabolic dysregulation. Despite postulations put forward to elucidate the mechanism underlying the association between early growth and later life metabolic disorders, it remains unclear what the dominant factor(s) would be, how any underlying mechanisms interact, or whether these mechanisms are truly causal.

Introduction
Growth, as the preparation of the living being for adaptation, survival, and reproduction, calls upon a highly effective and integrated system of interacting growth factors and hormones. Reports of rare individuals with genetic defects and various animal studies have allowed us to gain a deeper understanding of the roles of many of the genetic factors, hormones and growth factors involved.
Physiology of Growth

Growth requires a complex interaction of various genetic, nutritional, environmental and growth factors and hormones in a highly regulated and timely fashion. It is now clear that the growth hormone (GH) and insulin-like growth factor (IGF) signaling system plays an integral role in both pre- and postnatal growth [1]. GH, which is synthesized in the anterior pituitary, is the main regulator of IGF, through which it exerts in part its growth-promoting action. IGF is in turn regulated by six IGF-binding proteins (IGFBPs), namely IGFBP-1 to IGFBP-6. IGFBPs are themselves regulated by IGFBP proteases that cleave the IGFBPs to low-affinity fragments, and have important roles to play in modulating the effects of IGFs and IGFBP [2]. The regulation of growth and cellular proliferation is dependent on the ultimate interactions between IGFs and the IGF receptors.

In the fetus, GH is produced by the anterior pituitary gland from the end of the 1st trimester of gestation, and circulating levels of GH reach relatively high levels as the gestation progresses [3]. Although studies with anencephalic fetuses suggested that GH was not primarily involved in human fetal growth [4], the identification of GH receptor (GHR) expressions in the fetus suggests a possible role of GH on fetal growth [5]. This is supported by observations in that Laron dwarfs with inactivating GHR mutations are born 2 standard deviations (SDs) shorter than normal, and congenitally GH-deficient newborn babies have reduced birth length at birth [6]. Infants with congenital hypopituitarism are also observed to have birth lengths 0.8–1.7 SD below the mean [7], highlighting a contributory role of GH in prenatal growth. Despite these observations, the predominant regulator of fetal growth is mostly attributed to the IGF system. IGF production is largely independent of GH in the fetus. In the second trimester, both IGF-I and IGF-II are expressed in all human tissues with IGF-I continuously rising in the third trimester and beyond [8]. Knockout mice with either IGF-I or IGF-II deletion have severe growth retardation in utero with birthweight of only 60% of normal [9]. Mice with both IGF-I and IGF-II gene deletion simultaneously attain birthweight of only 30%, suggesting an additive role of both hormones in prenatal growth [10]. A case report of a human with IGF-I gene deletion exhibiting a pattern of growth parallel to
knockout mice suggested a similar role of the IGF system in prenatal growth in humans [11].

Besides the GH-IGF system, human placental lactogen, a protein hormone produced by the trophoblast cells of the placenta, shares structural homology with the GH, and has been shown to be involved in fetal metabolism and the growth and development of the placenta and the fetus [12]. Human placental lactogen promotes early embryonic growth and exerts its influence on the fetus by stimulating production of other hormones such as IGF-I and insulin [13].

Fetal insulin also plays a key role in the regulation of fetal growth and metabolism. Venous cord blood concentrations of insulin have been demonstrated to be significantly lower in small for gestational age neonates, and correlated with birth and placental weight and neonatal height [14]. In contrast, high fetal insulin in response to maternal hyperglycemia is responsible for the increased growth and macrosomia observed in infants born to mothers with gestational diabetes, demonstrating the integral role of insulin in fetal growth and development.

These hormonal interactions, together with multiple factors including maternal nutrition and health, placental and environmental factors on the backdrop of genetic susceptibility regulate growth and development of the fetus. Importantly, these interactions may herald an impact on the long-term health consequences in future adult life.

**Epidemiological Evidence of Early-Life Developmental Programming**

Barker et al. [15] observed more than 20 years ago that an association exists between the development of ischemic heart disease in adult life and men with low birthweights. Hales et al. [16] described that reduced growth in early life is strongly associated with impaired glucose tolerance and development of type 2 diabetes. Together, Hales and Barker described the ‘thrifty phenotype hypothesis’ which proposed that the epidemiological associations between poor fetal and infant growth and the subsequent development of type 2 diabetes and the metabolic syndrome result from the effects of poor nutrition in early life, which produces permanent changes in glucose-insulin metabolism [17]. The Dutch Famine Study described that the offspring of mothers exposed to the famine of 1944–1945 had an increased risk of later life glucose intolerance, coronary heart disease, a more atherogenic lipid profile, disturbed blood coagulation, increased stress responsiveness and more obesity [18]. Over the years, data have consistently proved the reproducibility of these epidemiological findings in various populations and ethnic groups. Studies of monozygotic twins where the diabetic twin had a lower birthweight further lend support that the environment plays a central role in mediating these associations [19]. Besides perinatal in-utero factors, epidemiological studies have indicated that postnatal factors in the form
of accelerated weight gain in early life also convey an increased risk of developing metabolic disorders in later life [20]. Although the association between the developmental plasticity of early life and the acquisition of metabolic diseases in adult life is well accepted, the underlying mechanisms affecting such an association remain unclear.

Genetic Factors Modulating Growth and Metabolic Disorder

Barker’s thrifty phenotype hypothesis places emphasis on the impact of environmental influence in the form of in utero nutrition on long-term programming of metabolic disorders. However, Hattersley and Tooke [21] proposed in 1999 in their fetal insulin hypothesis that this programming might be principally genetically determined. The basis for the fetal insulin hypothesis stems from the basis that genetic susceptibility is important for both birthweight and diabetes, and genes that reduce insulin secretion or increase insulin resistance will predispose to small babies as well as diabetes. In this hypothesis, insulin secretion and action are the main actor and the common pathway for the influence of genes. Insulin resistance and impaired insulin secretion are the common features of type 2 diabetes, and at the same time fetal insulin secretion is the main modulator of fetal growth in utero. This proposed genetically determined programming of the disorders of insulin secretion and action and the simultaneous effect on fetal growth have been supported in various single-gene disorders described in the literature. Glucokinase gene mutation, which causes mild β-cell dysfunction, can manifest as mild hyperglycemia. A mutation in the glucokinase gene in the mother resulted in a 601 grams increase in fetal size mediated through increased fetal insulin secretion in response to maternal hyperglycemia, but the same mutation in the fetus resulted in a 533 grams decrease in fetal size by decreasing fetal insulin secretion. When both mother and fetus had the glucokinase mutation, the two opposing effects cancelled out and the baby was of normal weight [22]. Other genes implicated in insulin secretion and fetal growth include the insulin promoter factor-1 gene. Homozygous mutation of this gene results in agenesis of the pancreas with markedly reduced fetal size to less than the 1st centile [23]. Homozygous mutations of the Kir6.2 and sulfonylurea genes result in persistent hyperinsulinemic hypoglycemia of infancy and are associated with increased birth size of more than 90th centile [24, 25]. The insulin VNTR genes are the other genes that have been implicated in both fetal growth and adult health outcomes [26]. Another study describing a polymorphism in the gene for IGF-I, which is associated with low birthweight showed an increased risk of type 2 diabetes and myocardial infarction, lending support to the hypothesis that genetic variation affecting fetal growth could account for the association between low birthweight and susceptibility to diabetes and cardiovascular disease in later life [27].
In this volume, Hwa et al. [pp. 43–55] outlined the role of the GH-IGF system and the impact of genetic defects of the GH-IGF axis on human linear growth. Defects in the GH-IGF axis leading to postnatal IGF-I deficiency and GH insensitivity syndrome include mutations in the GHR, signal transducer and activator of transcription (STAT5B) and IGFALS (acid labile subunit, ALS) genes. The identification and evaluation of genetic defects in the GH-IGF axis have provided proof of principle and greatly enhanced our understanding of the critical importance of the GH-IGF system in human linear growth. The general prevalence of these specific genetic mutations is however generally low, and could identify only a small proportion of growth defects, therefore suggesting the possibility of other mutations in the promoter or other regulatory parts of the genes that are currently unknown. Moreover, the interaction of these genes with the environment and other signaling pathways such as those affecting the immune system which may affect growth are also just emerging, providing postulations that the GH-IGF axis does not act as an isolated factor in growth disorders. For example, the GHR is a cytokine receptor belonging to the same superfamily of receptors as the interleukins and interferon. All of those receptors signal through the JAK STAT system, so knockout of the STATs affects both GH and cytokine action. Therefore, the blocking of GH action results in growth failure, and the accompanying blocking of the cytokine action may result in immune defects. These observations of how genetic defects in the GH-IGF axis disrupt the ability of the GHR to signal through its JAK STAT pathway and the resulting interaction with the immune system via cytokine signaling may provide an explanation to how chronic inflammatory diseases affecting immune system may impact on growth, highlighting the complex interaction between the GH-IGF axis and other endocrine and immunological processes in the human body to effect growth.

Taken together, these specific genes have only been able to explain a small part of the association with fetal growth and overall metabolic disease risk in future life. It is likely that the association between early-life plasticity and future development of metabolic disorder necessitates a more complex interaction of various factors in utero and environmental influences on a background of genetic predisposition.

**Epigenetic Programming**

Epigenetics is the changes in heritable gene expression caused by alterations independent of changes in the genotype. The main epigenetic mechanisms include DNA methylation and modifications of histones that package the DNA including acetylation. Animal studies have indicated that early-life environmental influences can affect epigenetic changes in the DNA methylation that may
have later life phenotypic consequences [28]. A study utilizing Agouti viable yellow allele mice (Avy), which are obese and hyperinsulinemic, demonstrated that a maternal diet enriched with methyl donors caused hypermethylation in the offspring of Avy mice resulting in the masking of the Avy gene with the offspring being leaner and not hyperinsulinemic [29]. In recent years, a study in humans demonstrated that individuals who were prenatally exposed to the Dutch Winter famine in 1944–1945 had, 6 decades later, less DNA methylation of the imprinted IGF-II gene compared with their unexposed, same sex siblings. The association was specific for periconceptional exposure, reinforcing that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks [30].

In this volume, Netchine et al. [pp. 65–73] described specifically the loss of DNA methylation at the imprinted control region leading to the development of the Russell-Silver syndrome, which is characterized by intrauterine and postnatal growth retardation; in contrast, the gain of such DNA methylation results in Beckwith-Wiedemann syndrome which is characterized by overgrowth syndrome with enhanced childhood tumor risk, providing further validation of how epigenetic processes may affect growth. Godfrey et al. [this volume, pp. 57–63] highlighted the effect of epigenetic processes, in particular DNA methylation, on the risk of developing common non-communicable diseases in later life. Various animal studies have further highlighted role of endocrine and nutritional interventions during early postnatal life in reversing the phenotype in the epigenetic changes, providing the proof of principles that relate maternal nutritional deficiencies and epigenetic changes and the associated phenotypic expression. Although epigenetic processes do offer an additional dimension to elucidating the mechanism underlying early-life exposure and later life health risks, and various animal studies do provide proof of causality on the role of epigenetic changes in phenotypic expressions, the understanding of how nutrition or endocrine interventions may influence epigenetic regulation of genes is only just beginning, and whether these epigenetic changes are markers versus whether they can be causally related to disease outcomes in humans remains to be fully elucidated.

**Other Postulated Mechanisms**

Several other mechanisms have been proposed to elucidate the mechanisms underlying early growth and later life development of metabolic disorders. The maternal glucocorticoid programming is one of these. Studies using animal models have described decreased birthweights in rats prenatally exposed to synthetic glucocorticoids or through inhibition of the placental 11β-hydroxysteroid dehydrogenase type 2 (HSD2) which may induce permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal axis (HPA)
activity and behavior resembling anxiety [31]. In humans, 11β-HSD2 gene mutations cause low birthweight and reduced placental 11β-HSD2 activity associated with intrauterine growth retardation. Low birthweight babies were also found to have higher plasma cortisol levels throughout adult life, suggesting HPA axis programming [32].

Maternal hypoxia is another suspected mediator of increased vulnerability to metabolic and cardiovascular diseases [33]. Offspring of mothers who were exposed to a high-altitude environment with chronic hypoxia were growth restricted. Further evidence illustrated the direct detrimental effects of prenatal hypoxia on endothelial function [34], which was independent of maternal nutrition restriction, further supporting the possible role of hypoxia in placental function, fetal growth and metabolic programming.

Placental dysfunction may also play a central role in fetal programming, and the failure of the maternal-placental nutrient supply to match fetal requirements may incite developmental plasticity and adaptations to culminate in the development of metabolic diseases [35]. The basis for this hypothesis stems from the observations that alterations in placental growth and vascular resistance, altered nutrient and hormone metabolism, and changes in nutrient transfer and partitioning between mother, placenta and fetus all have important effects on the fetal adaptations that are thought to be central to programming. The implication of the hypothesis is that optimizing placental structure and function may well have lifelong health benefits for the offspring. Although well described, epidemiological data linking pathological placental changes and development of metabolic diseases in the offspring are currently lacking.

**Leptin and the GH-IGF Axis**

One of the key components of Barker’s hypothesis described that insulin resistance and associated reductions in muscle mass represent a trade-off between the development of muscle and brain masses under conditions of energetic deprivation in the fetus, with adaptive sparing of the brain tissue at the expense of muscle mass that are ultimately reflected in reduced birthweight [36]. This trade-off, or preferential rationing of energy stores, may be a plausible mechanism ultimately predisposing these individuals to later life metabolic disorders. Many of the other key modulators of energy metabolism including insulin, GH-IGF and the HPA axis are important modulators of fetal growth and birth sizes. In states of chronic energy deficiency, decreased IGF levels and increased GH secretion are often observed [37]. Leptin plays an integral role in signaling energy availability and mediating neuroendocrine response to energy deprivation states in humans. In a study performed on hypothalamic amenorrhea women with chronic energy deficit, a state signified by hypoleptinemia, leptin administration which increased serum leptin
levels to within normal physiological levels after 1 month of treatment was associated with an increase in total IGF-I levels, with a trend to increasing free IGF-I and IGFBP-3 [38], suggesting a key role of leptin in modulating IGF-I and the GH-IGF axis in the energy deprivation state. It is interesting to speculate a possible role of leptin in modulating the GH-IGF system in women in gestation during periods of malnutrition and energy deprivation, and the long-term effects of such modulation on fetal growth and developmental programming. The role of leptin in energy signaling and modulating growth factors especially in gestating women may have implications on possible developmental programming of the fetus of which mechanistic issues remain to be fully elucidated.

Uncertainties

The replication of data in different populations and ethnicities proves conclusively that an association exists between early-life and future development of metabolic disorders. Despite postulations put forward to elucidate the mechanism behind the association, it remains inconclusive if these mechanisms are truly causal. It is also possible that the association is the result of the interplay between a multitude of differing mechanisms and influences, both inherent and environmental. It remains uncertain as to how these different mechanisms interact, let alone establishing the predominant factor amongst these differing processes. Moreover, even in the situation where a dominant mechanism truly exists and is causal, it is unknown if such early-life developmental programming will be reversible. If this early-life programming is irreversible, the only available intervention will nonetheless be restricted to a universal effort in improving women’s reproductive health through better nutrition, sanitation and prenatal care. Exhaustive efforts to unravel and debate mechanistic issues behind developmental programming might be relegated to a sterile intellectual exercise with little implications on intervention options to individuals already exposed to poor developmental programming. The relative importance of developmental programming in the pathogenesis of metabolic disorders in comparison to traditional risk factors such as obesity, diet, lack of physical activity, and smoking, also remains unknown.

Nonetheless, the avalanche of data in the last few decades on developmental programming and metabolic disorders has shed new light on the possible pathogenesis of metabolic disorders. Further research will hopefully not only elucidate the causative mechanism underlying such an association, but also allow us to gain insight into the possible interventions we can adopt to curb the ever growing problem of metabolic disorders.
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References


