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The influence of placental hormones and insulin-like growth factors in fetal growth and development

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Abstract

The role of the placenta in fetal growth and development is achieved largely through hormones that regulate fetal and maternal metabolism. Thus the endocrine function of the placenta is as important as the exchange of nutrients and waste products between the mother and the fetus. Fetal growth and development, largely depends on the nutrients and metabolites found in the mother's body. However, the fetus may alter intrauterine homeostasis and its process of growth and development through hormones. Aneventual dysfunction at this level can lead to impaired fetal growth and development, which can translate to fetal intrauterine growth restriction. A better understanding of these mechanisms may lead to a future decrease in the incidence of such cases.
Keywords: *insulin growth factor-I, fetal growth, pregnancy*

Introduction

Placenta plays an important role in fetal growth and development, because this is the organ by which exchanges the nutrients, metabolites and gases between the mother and the fetusare assured. An equally important role of this organ, however, is to ensure a certain fetal and maternal hormonal environment, without which fetal growth and development is not possible. During pregnancy, the placenta, the fetus and the mother are involved in the synthesis and secretion of a large number of steroid hormones (i.e. progesterone, estrogen), protein hormones (i.e. gonadotropin releasing hormone, corticotropin releasing hormone, thyrotropin releasing hormone, somatostatin, human chorionic gonadotropin, human chorionic somatomammotropin, human chorionic thyrotropin, human chorionic adrenocorticotropin, growth hormone, growth hormone releasing hormone, alpha-fetoprotein, relaxin, prolactin, cytokines and growth factors, inhibin, activin, follistatin, opiates, and atrial natriuretic peptide), thromboxanes and prostaglandins[(1)].

Human placental growth hormone

In humans, growth hormone can be produced in the pituitary somatotropic cells, or in the syncytiotrophoblast. The chemical structure of the placental growth hormone, differs from the pituitary growth hormone by 13 aminoacids. The production of placental growth hormone, gradually increases during pregnancy, and after 15 weeks of pregnancy, it is higher than the production of pituitary growth hormone. At the time of delivery, maternal pituitary growth hormone serum levels are close to zero. The main function of the placental growth hormone is to increase the maternal seric glucose levels, and its secretion is not influenced by the placental release-hormones. An increase in maternal seric level of growth hormone determines an increase of the insulin growth factor-I (IGF-I). The placental growth hormone is not present the fetal circulation, but it can influence fetal growth by modulating energetic metabolism and by increasing maternal lipolysis and gluconeogenesis[(1)]. Inflammation in the placenta may interfere with hormone production process and may even influence the placenta shape[(2)].

IGFs in fetal and neonatal development

IGF-I and IGF-II are peptide molecules consisting of a single chain of amino acids, involved in fetal and neonatal growth and development. These molecules bind to specific IGF receptors (IGF-1R and IGF-2R), the insulin receptor (InsR) and a hybrid receptor IGF-1R-InsR[(1)].

IGF-I is the molecule through which growth hormone exerts its action. This is a small peptide molecule of 70 amino acids with a molecular mass of 7647 daltons. More than 99% of these molecules are bounded to plasma proteins and carriers. IGF-I is produced mainly in the liver by the action of growth hormone, and is released into the circulatory system. Smaller amounts of IGF-I are synthesized locally in other tissues, with paracrine or autocrine effects. Circulating IGF-I has

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systemic effects, providing a uniform growth pattern during organ and tissue development. Peripheral tissue production of IGF-I is regulated by the growth hormone and other molecules secreted by nearby cells[3].

IGF-I exerts its actions by binding to a specific receptor found in every cell of the body. Each cell contains between 20,000 and 35,000 IGF-I receptors. The growth hormone, thyroxine, platelet-derived growth factor, fibroblast growth factor and other growth factors acts to regulate the IGF-I receptor number. The IGF-I receptor consists of two α subunits, which contain the binding site for the IGF-I molecule, and two β transmembrane subunits. When the IGF-I molecule binds to the receptor, conformational changes in the receptor structure will lead to the activation of intracellular signaling pathways (tyrosine-kinase activation) [3]. Finally, after the phosphorylation of intracellular signaling molecules, the RAS - microtubule-associated protein kinases will be activated, and the cell growth will be stimulated.

Another intracellular signaling pathway that is activated after the binding of IGF-I molecule to its receptor, is the tyrosine kinase pathway B, which stimulates protein synthesis,tissue differentiation andinhibits cellular apoptosis[3].

The IGF-I receptor may be present in larger amounts than normal,in tumoral cells. The IGF-II receptor is less important in terms of cell growth, but it modulates the effects of IGF-I and IGF-II molecules. IGF-II receptor consists of a single peptide chain, and it binds IGF-II with an affinity about 80 times greater than IGF-I[3].

IGF-I and IGF-II molecules are bounded to specific plasma proteins (IGFBP). There are six types of IGF binding proteins (IGFBP-1 to IGFBP-6), and their affinity for IGF molecules is greater than that of the IGF-R, which is the reason why only a very small fraction of IGF molecules circulates free (less than 1%). IGFBP are also present in the extracellular compartment. Their main role is to regulate the IGF activity by controling the IGF free fraction. IGFBP-3 is found in the highest concentration and has the highest affinity for IGF-I. Because the serum level of IGFBP-1 may vary greatly in 24 hours this is the protein responsible for most of the effects of IGF-I[3].

The seric level of IGFBP-1 varies greatly throughout the day, since its production is inhibited by the food intake and insulin and stimulated by fasting. The administration of IGFBP-1 in animals results in increased blood glucose levels, hence this protein may be involved in the regulation of carbohydrate metabolism. The dosage of serum IGFBP-1 is currently used to assess hepatic sensitivity to insulin in patients with type 2 diabetes mellitus[4].

IGF effects

In vitro actions of IGF-I include stimulation of deoxyribonucleic acid (DNA) and protein synthesis, stimulation of cellular growth, glucose oxidation, the transport of fatty acids and glucose, stimulation of lipogenesis. IGF-I is an inhibitor of programmed cell death in the nervous tissue and in the haematologic system. IGF-I also inhibits follicular cell apoptosis. IGF-I enhances the action of luteinizing hormone and follicle-stimulating hormone on follicular cells, the action of adrenocorticotrop hormone on the cortical cells of the adrenal glands, the secretion of testosterone from Leydig cells, the action of tyroid stimulating hormone on the thyroid epithelial cells. IGF-I enhances cell differentiation in myoblasts, chondrocytes and osteoblasts, stimulating the synthesis of proteins involved in these processes, such as osteocalcin produced by osteoblasts and myogenin produced by muscle cells[5].

IGF-I has an important role in tissue repair process. It has been noticed that the cells involved in lesions of the nervous tissue, muscle, cartilage and endothelium, secrete large amounts of IGF-I that will stimulate protein and DNA synthesis by autocrine and paracrine effects[3].

The effects of IGF-I administration in humans includes, low blood sugar, stimulating protein syntesis and inhibition of proteolysis, anabolic effects on bone in patients with osteoporosis, increased plasma concentrations of IGF-I binding protein type 2, increased glomerular filtration rate of about 25 percent, cancellation of glucocorticoid effects on protein metabolism. The effects of IGF-I administration are increased by the administration of growth hormone[3].

IGFs in pregnancy

Maternal serum levels of IGF-I may also influence fetal growth by controlling the placental flow of nutrients to the fetus. A lower seric level of placental growth hormone was observed in pregnant women with growth restricted fetuses[6]. Fetal hyperinsulinemia encountered in maternal gestational diabetes (i.e. often associated with maternal obesity)[7] was associated with high levels of IGF, increasing the risk of fetal macrosomia[8].

IGF-I has a very important role in fetal growth and development. This is proven by the fact that fetuses with genetic defects that affect IGF-I structure and its receptor, are growth restricted, may develop metabolic disorders or developmental delay, may suffer from sensory deficits and microcephaly.

In the womb, fetal metabolic needs are covered by the transfer of carbohydrates and nutrients from the mother through the placenta. IGF-I concentration in the fetal serum is regulated by the flow of nutrients to the fetus. Insulin is the main factor which regulates the rate of hepatic synthesis of IGF-I and IGFBP-1. When the serum insulin concentration is low, hepatic synthesis of IGF-I decreases and the production of IGFBP-1 is stimulated. IGFBP-1 will bind free to IGF-I molecules, thus decreasing its bioavailability. In this way, the fetal energy metabolism is mainly focused on glycolysis, and not lipolysis, being known the fact that the fetus has a reduced ability to produce energy by fatty acid oxidation. The fetal mechanism of regulating IGF-I

production is different from that in adults, where the IGF-I synthesis is controlled by the growth hormone. The transition from the fetal to the adult mode of IGF-I synthesis is made gradually, as the growth hormone binding protein is being produced. In this way, the influence of the growth hormone over the process of IGF-I synthesis is completed in the second year of life[9].

IGF-I plays an important role in the growth and development of the fetal nervous system, facilitating the use of glucose at this level, in cell maturation and differentiation, in nerve myelination and cell proliferation processes. In cases where anomalies in the genes encoding IGF-I synthesis were present, microcephaly and psychosomatic development delay were very common. In patients with growth hormone resistance syndrome, IGF-I is effective for improving the growth pattern, increasing the head circumference and the brain substance[9].

Fetal adipose tissue begins to develop after 24 weeks of pregnancy. Adipose tissue is a metabolically active organ, receptors for insulin, IGF-I and other hormones being present in the mature adipose cells. This type of tissue is able to synthesize a large number of molecules acting on the energy metabolism by hormonal or paracrine mechanism. Dysfunctional adipose tissue has been associated with type 2 diabetes and insulin resistance syndrome. Fetal adipose cells contain as many insulin receptors as IGF-I receptors, while the mature adipose cell contains 10 times more insulin receptors than IGF-I receptors. This suggests that IGF-I is important in growth and differentiation of fetal adipocytes, and they must be initially under the influence of IGF-I in order to support adipogenesis induced by insulin. Therefore, insulin sensitivity of the fetal adipose tissue increases with gestational age[9].

The role of IGF-I in pulmonary organogenesis has been proven mostly from studies in mice with different mutations in the genes encoding the synthesis of IGF-I molecule. Mice with a homozygous deletion of the gene are born with hypotrophic lungs, and have a high rate of postnatal death from respiratory failure. Also, it has been observed that the addition of IGF-I *ex vivo* to a lung derived from embryos deficient in IGF-I, resulted in intrapulmonary airway remodeling, increased number of alveolar septa and maturation of the epithelium. In the embryonic lung tissue, IGF-I is synthesized by macrophages, type II pneumocytes and mesenchymal cells[9].

The influence of IGF-I on fetal growth and development has been highlighted from studies in premature infants. Their serum IGF-I concentration is about 5 times lower than that of the fetuses of the same gestational age *in utero*, this being due mostly to changes in nutrient intake, hypoxia and inflammatory molecules. Preterm neonates can not use nutrients efficiently, given the fact that the transition from an energy metabolism that relies mostly on glycolysis (i.e. *in utero*) to one based on the predominance of oxidative phosphorylation is delayed. In adults, serum levels of IGF-I are correlated with protein intake, independent of caloric intake, ensuring in this way, optimum use of proteins. Therefore, the seric level of IGF-I can be used as an indicator of the nutritional status. It was noticed that although a high protein diet was used in preterm neonates, there was no increase in serum IGF-I levels nor asatisfactory weight gain, up to about 30 weeks of age. This proves an inefficient use of nutrients in preterm neonates. The persistence of low serum levels of IGF-I correlates with the great complications of preterm neonates such as retinopathy of prematurity, lung dysplasia, impaired growth and development, impaired development of the nervous system[9]. Another important fact that needs further research is the influence of IGF and other placental hormones levels in early pregnancy failure[10].

Conclusions

Human placental growth hormone and IGFs play a key role in the fetal growth and development process. The way that the fetus can modify the intrauterine environment and its growth pattern is not entirely understood but hormones surely have a central role. Among these molecules, IGFs seem to interfere the most with the metabolic preocesses involved in human growth from the beginning all the way to the adult life. ■

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