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Insulin and the IGF system in the human placenta of normal and diabetic pregnancies

Ursula Hiden, Elisabeth Glitzner, [...], and Gernot Desoye

Additional article information

Abstract

The insulin/insulin-like growth factor (IGF) system regulates fetal and placental growth and development. In maternal diabetes, components of this system including insulin, IGF1, IGF2 and various IGF-binding proteins are deregulated in the maternal or fetal circulation, or in the placenta. The placenta expresses considerable amounts of insulin and IGF1 receptors at distinct locations on both placental surfaces. This makes the insulin and the IGF1 receptor accessible to fetal and/or maternal insulin, IGF1 and IGF2. Unlike the receptor for IGF1, the insulin receptor undergoes a gestational change in expression site from the trophoblast at the beginning of pregnancy to the endothelium at term. Insulin and IGFs are implicated in the receptor-mediated regulation of placental growth and transport, trophoblast invasion and placental angiogenesis. The dysregulation of the growth factors and their receptors may be involved in placental and fetal changes observed in diabetes, i.e. enhanced placental and fetal growth, placental hypervascularization and higher levels of fetal plasma amino acids.

Keywords: insulin, insulin-like growth factors, placenta, diabetes

Introduction

The placenta is a fetal organ located at the interface between the maternal and fetal circulation, fulfilling a spectrum of fundamental functions for pregnancy. Most central is the supply of nutrients and oxygen to the fetus and the production of a range of hormones and growth factors that, when released, may affect mother or fetus or both. In addition, placental processes may be controlled in a paracrine or autocrine fashion.

Conversely, hormones, growth factors and substrate present in the maternal and the fetal circulation may tightly regulate placental development. Notably the insulin/insulin-like growth factor (IGF) system, i.e. insulin, IGF1, IGF2 and the IGF-binding proteins IGFBP1 and IGFBP3, are implicated in the regulation of fetal and placental growth and development. Such actions are mediated through their receptors, i.e. insulin and IGF1 receptors, which are expressed on distinct placental surfaces. Hence, dysregulation of insulin and IGFs may have profound effects on placenta and fetus.

The insulin/IGF system

The peptide hormones insulin, IGF1 and IGF2 mediate a variety of metabolic and mitogenic effects by binding to their specific receptor tyrosine kinases present on the surface of target tissues and cells. Because of their considerable structural homology, a distinct overlap exists in binding affinity between receptors on the one hand and insulin and IGFs on the other hand. However, at physiological concentrations, insulin and IGF1 exclusively bind to their cognate receptors, i.e. the insulin receptor (IR) and the IGF1 receptor (IGF1R), respectively. In contrast, IGF2 binds to the IGF1R and, in particular in embryonic and cancer tissues and cells, to an IR isoform that lacks exon 11 and is therefore denoted as IR 11– (Frasca et al. 1999). The affinity of IGF2 to IR 11– is only slightly lower than that of insulin (EC_{50} of 0.9 vs. 0.2 nM), whereas IGF1 binding to IR 11– has no physiological relevance (EC_{50} > 30.0 nM). The binding affinity of IGF2 to IGF1R is nearly comparable to that of IGF1 (EC_{50} 0.6 vs. 0.2 nM), whereas insulin weakly binds (EC_{50} > 30.0 nM) (Pandini et al. 2002).

Placental IGF1 and IGF2 expression

IGF1 and IGF2 are important growth factors in fetal development. Both are synthesized in placenta and fetus with a considerable overlap in the location of both IGFs in the various placental cell types, in particular in the mesenchymal cells such as macrophages and endothelial cells, with little change throughout gestation. However, there is a clear difference and developmental change in the trophoblast compartment. Whereas IGF1 is present in syncytiotrophoblast and cytotrophoblast at all stages in

gestation, IGF2 is not found in the syncytiotrophoblasts. Its expression in the villous and extravillous cytotrophoblasts in the first trimester becomes undetectable at term (Hill et al. 1993; Thomsen et al. 1997; Birnbacher et al. 1998; Han and Carter, 2000; Dalcik et al. 2001). It is unclear if the placenta-derived IGFs serve local purposes by paracrine or autocrine regulation, or if they are secreted into the maternal or fetal circulation.

IGFBPs

IGF-binding proteins (IGFBPs) are further players in the IGF system. They are key modulators of the ligand–receptor interaction. The six human IGFBPs described so far circulate in the plasma and bind IGFs with a higher affinity than the receptors, thereby sequestering them from receptor binding (Hwa et al. 1999; Allan et al. 2001; Denley et al. 2005). This interaction facilitates endocrine IGF transport and prolongs the half-life of circulating IGFBP-bound IGFs (Hwa et al. 1999; Denley et al. 2005). In addition, IGFBPs can be associated with cell membranes or extracellular matrix. This allows them to maintain a local pool of IGFs. Because of similar affinities of IGFs for cell-

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IGFBPs can be associated with cell membranes or extracellular matrix. This allows them to maintain a local pool of IGFs. Because of similar affinities of IGFs for cell- or membrane-bound IGFBPs and for their receptors, the balance in the amount of both will be the main determinant of the prevailing binding site of IGFs (Han & Carter, 2000). Post-translational IGFBP modification by phosphorylation, glycosylation and specific proteolysis (Clemmons, 1998) can further modulate IGF binding. Phosphorylation and proteolysis are altered during pregnancy, resulting in a preponderance of IGFBPs with lowered affinities towards IGFs, thus increasing system-wide IGF bioavailability (Forbes & Westwood, 2008). In nonpregnant women, the majority of IGF1 is part of a ternary complex together with IGFBP3 and acid-labile subunit (Forbes & Westwood, 2008). The serum of pregnant women contains the placenta-derived IGFBP3 protease (Deal, 1992). It cleaves IGFBP3 into smaller fragments with lower affinities for IGFs, rendering IGFs available for binding to their receptors in mother and placenta (Giudice et al. 1990; Hossenlopp et al. 1990; Davenport et al. 1992). Placental alkaline phosphatase dephosphorylates serum IGFBP1 in pregnant women, reducing its affinity for IGF1 (Westwood et al. 1994), whereas IGFBP1 affinity for IGF2 remains unchanged. IGF2 binding to IGFBP1 is modulated by proteolytic cleavage of non-phosphorylated IGFBP1 by matrix metalloproteases MMP3 and MMP9 at the maternal–fetal interface (Coppock et al. 2004).

Decidual cells of the basal plate region express mRNA of all six IGFBPs in the second and third trimester, with IGFBP1 being the most abundant. In the placenta, IGFBP3 is expressed in the extravillous cytotrophoblasts (Hamilton et al. 1998). In maternal Type 1 diabetes (T1D), IGFBP3 mRNA is increased (Liu et al. 1996). Maternal serum and cord blood levels of IGFBP1 and -3 are altered in pregnancies complicated by diabetes. Studies examining IGFBP1 concentrations in offspring from T1D or gestational diabetes mellitus (GDM) mothers produced inconsistent results, with either elevated (Yan-Jun et al. 1996; Lindsay et al. 2007) or decreased (Culler et al. 1996; Lindsay et al. 2007) levels. An association between maternal diabetes and cord IGFBP1 phosphorylation state has been discussed as well (Loukovaara et al. 2005b).

In the cord blood, increased IGFBP3 levels in pregnancies complicated by T1D correlate with IGF1 levels and the incidence of macrosomia (Nelson et al. 2008). This is consistent with the observation that IGF1 and IGFBP3 levels directly correlate with birth weight both in the healthy and in the diseased state (Osorio et al. 1996; Ong et al. 2004; Nelson et al. 2008).

Diabetes in pregnancy and the insulin/IGF system

The placenta shows several alterations in maternal diabetes, and the insulin/IGF system has been implicated in several of these (Desoye & Shafrir, 1996; Desoye & Myatt, 2004; Desoye & Hauguel-de Mouzon, 2007;Desoye et al. 2008). GDM and T1D are characterized by dysregulation of various factors in the maternal, but also in the fetal, circulation, and in the placenta. These include components of the insulin/IGF system, i.e. insulin, IGF1, IGF2 and the IGF-binding proteins IGFBP1 and IGFBP3 (see Fig. 1).

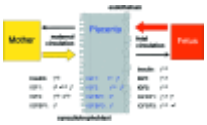

Fig. 1

The placenta is exposed to metabolites and hormones of mother and fetus. Diabetes (T1D and GDM)-associated changes in levels of insulin, IGF1, IGF2, IGFBP1, IGFBP3 in maternal and fetal blood and in the placenta may influence placental function. Higher…

The placenta is richly endowed with IR and IGF1R, and serves as the tissue of origin for isolation of the receptor proteins. Both receptors are located on distinct placental surfaces, thus enabling maternal and/or fetal insulin, IGF1 and IGF2 to affect placental function and development. Therefore, in a pregnancy complicated by diabetes, altered insulin, IGF and IGFBP levels are most likely to influence placental cells in a manner different from normal pregnancies. These changes in the circulating levels of the growth factors may be superimposed by additional alterations in other components of the system such as IGFBPs, receptor expression, receptor activation and signalling.

IR expression in the placenta

IR and IGF1R expression in the placenta is more complicated and restricted to special areas than has long been thought. Their location varies with gestational age. IR is

expressed in a spatio-temporal manner. In the first trimester of pregnancy, IRs are predominantly expressed on the microvillous membrane of the syncytiotrophoblast, directed to the maternal circulation and, hence, maternal insulin. Some IRs are also present in the villous cytotrophoblasts. In contrast, IRs at term are mainly expressed on the placental endothelium directed to the fetal blood. Therefore, IR expression shifts throughout pregnancy from the surface facing the maternal circulation to that facing the fetal circulation (Desoye et al. 1994, 1997; Hiden et al. 2006). Tissue-resident macrophages (Hofbauer cells) also express IR.

The spatio-temporal change in receptor expression is paralleled by a change in total receptor activation, which results in accompanying changes in intracellular downstream effect as identified by insulin-induced gene expression. In isolated primary first trimester trophoblasts with high levels of IR, insulin altered the expression of 236 genes, whereas in primary term trophoblasts with lower IR levels, the effect of insulin expression was minimal (six regulated genes). At that time in gestation most IR are expressed on the placental endothelium, which readily responds to insulin stimulation (146 regulated genes). Hence, the shift in IR expression from the trophoblast to the endothelium represents also a shift in regulation of insulin effects from the mother to the fetus (Fig. 2) (Hiden et al. 2006).

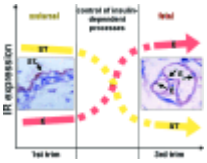

Fig. 2

The spatio-temporal change in placental insulin receptor (IR) expression suggests a shift in regulation of placental insulin effects from mother to fetus. In the first trimester, IRs are predominantly expressed on the syncytiotrophoblast (ST) facing the ...

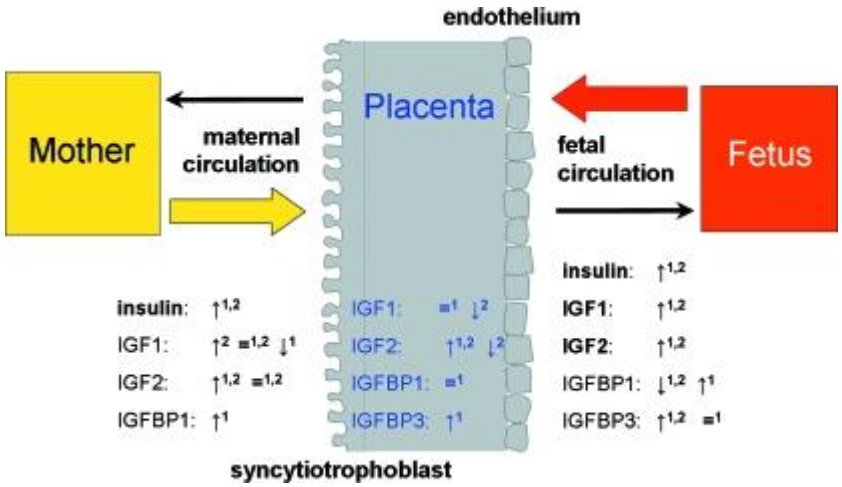
endothelium
Placenta
Mother
maternal circulation
fetal circulation
Fetus
insulin: ↑1,2
IGF1: ↑2 =1,2 ↓1
IGF2: ↑1,2 =1,2
IGFBP1: ↑1
IGF1: =1 ↓2
IGF2: ↑1,2 ↓2
IGFBP1: =1
IGFBP3: ↑1
insulin: ↑1,2
IGF1: ↑1,2
IGF2: ↑1,2
IGFBP1: ↓1,2 ↑1
IGFBP3: ↑1,2 =1
syncytiotrophoblast

Fig1:

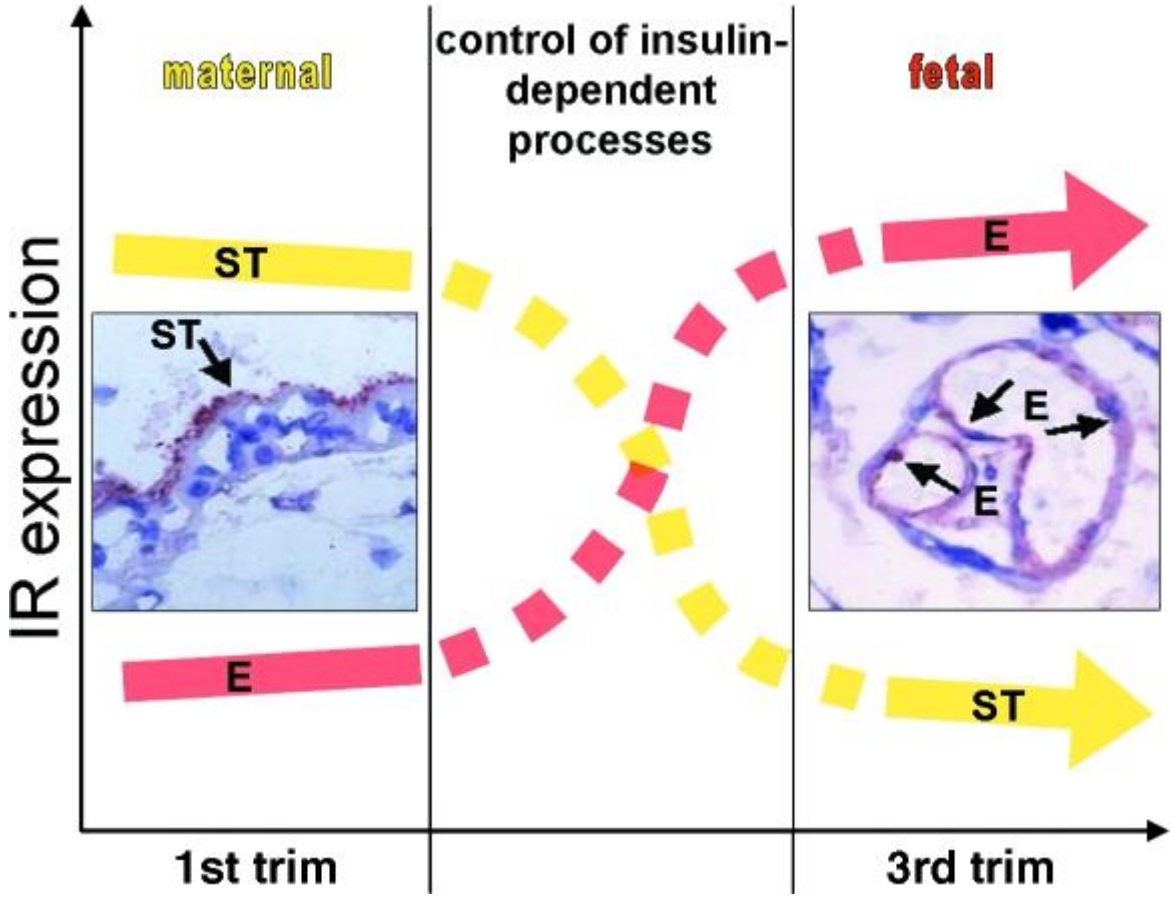
maternal
control of insulin-dependent processes
fetal
IR expression
ST
ST
E
E
E
E
ST
1st trim
3rd trim

Fig.2