Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Placental peptides regulating islet adaptation to pregnancy: clinical potential in gestational diabetes mellitus

Sian Simpson, Lorna Smith and James Bowe

Pregnancy involves a progressive increase in insulin resistance and the β-cells must adapt to compensate and prevent gestational diabetes (GDM). In this review we discuss the evidence for placental peptides, including placental lactogen, hepatocyte growth factor, adiponectin and leptin, playing a role in the islet adaptation to pregnancy. The difficulties of translating data from rodent models into human pregnancy are covered and we summarise studies investigating associations between serum placental peptides and GDM risk. In conclusion, current data support important roles for placental peptides interacting to support β-cells during pregnancy, however mechanisms involved in humans are unclear. Further work in humans is required, but placental peptides have clinical potential from both a diagnostic and therapeutic perspective.

Address
Department of Diabetes, School of Life Course Sciences, King's College London, Guy's Campus, London SE1 1UL, UK

Corresponding author: Bowe, James (james.bowe@kcl.ac.uk)

Current Opinion in Pharmacology 2018, **43**:59–65

This review comes from a themed issue on **Endocrine and metabolic diseases**

Edited by **James Bowe** and **Shanta Persaud**

https://doi.org/10.1016/j.coph.2018.08.004

Introduction

During a healthy pregnancy insulin sensitivity falls with gestational age. This physiological change prioritises the delivery of glucose across the placenta for fetal development. However, this poses a dilemma for the maternal metabolism to balance providing for the energy requirements of the growing fetus, while simultaneously maintaining maternal glucose homeostasis. In a healthy mother the insulin resistance is countered by adaptive changes in pancreatic islets to allow increased insulin secretion, including an increased β-cell mass. Failure of the insulin-releasing β-cells to sufficiently adapt and compensate for the increased metabolic demand in pregnancy leads to development of glucose intolerance, hyperglycaemia and gestational diabetes mellitus (GDM).

Gestational diabetes

The rapid worldwide increase in the prevalence of type 2 diabetes mellitus (T2DM) is well-documented, but it is less appreciated that the incidence of GDM is also rapidly rising in parallel with the T2DM pandemic. It is currently estimated worldwide that 21.3 million pregnancies per year (16.2% of total pregnancies) are affected by some form of hyperglycaemia, with 86.4% of those cases due to GDM (IDF Diabetes Atlas: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8th-edition.html). Maternal GDM has consequences for the mother and developing fetus, including placental insufficiency because of preeclampsia, macrosomia (birth weight >90th centile), birth injury and neonatal hyperinsulinism and hypoglycaemia. Epidemiological and experimental studies have also demonstrated that the GDM intra-uterine environment can increase susceptibility of the offspring to later life T2DM and cardiovascular disease, whilst in mothers GDM is associated with the subsequent development of T2DM.

At present GDM is diagnosed through routine oral glucose tolerance testing at 24–28 weeks of gestation, once impaired glucose tolerance has developed. Therapeutically GDM is primarily treated with either insulin injections or metformin, though the use of insulin analogs which do not cross the placenta have also been suggested [1]. Given the range of acute and potentially chronic consequences of GDM for both mother and child, there is currently great interest in developing diagnostic tools for predicting high GDM risk earlier in pregnancy, thus allowing time for intervention. Additionally, the identification of additional therapeutic targets is of keen interest for investigation.

Placental peptides

GDM is primarily the result of insufficient islet adaptation and an inability to increase insulin secretory capacity to compensate for increased insulin resistance. In normal pregnancy β-cells adapt in several respects to increase functionality. In rodent models these mechanisms include increased insulin synthesis and release, increased glucose responsiveness, increased cell–cell communication, hypertrophy, increased proliferation and reduced apoptosis, resulting in an overall increase in β-cell mass.

The β-cell adaptation in human pregnancy is more controversial, particularly concerning β-cell proliferation, but broadly speaking a similar pattern is observed with increased insulin release and increased β-cell mass. Thus, understanding the signals and mechanisms that regulate the islet adaptation to pregnancy and the reasons for these mechanisms failing in GDM warrants further investigation.

The placenta plays many essential roles during pregnancy, including supporting and protecting the fetus, and the supply of nutrients and gas exchange. The placenta also acts as an essential endocrine organ, producing and releasing hormones and mediators into the maternal circulation to maintain pregnancy. Increasing evidence suggests that several placental hormones play a role in communicating with maternal β-cells to regulate the islet adaptation necessary for a healthy pregnancy.

The effects of steroid hormones released from the placenta, including oestrogens, progestogens and glucocorticoids, on glucose homeostasis are complex and still controversial. Oestrogens have been implicated in the islet adaptation to pregnancy, through both direct and indirect protective effects on β-cells [2]. Effects of progestogens appear to vary with concentration and the presence of other hormones [2], and further work is required to understand their role. The placenta also releases a much wider range of peptide hormones into the maternal circulation that may influence the islet adaptation to pregnancy. Despite β-cells expressing cognate receptors for many of these ligands, only a few have been investigated for possible effects during pregnancy. Thus, this review will summarise the placental peptides currently thought to play a role in the islet adaptation to pregnancy and discuss whether these peptides may represent useful biomarkers for early determination of GDM risk.

Lactogenic hormones

The lactogenic hormones, prolactin (PRL) and placental lactogen (PL), are the most extensively studied hormones involved in the islet adaptation to pregnancy. During early pregnancy PRL is released from the maternal anterior pituitary, but following placentation maternal circulating levels of PRL fall and PL released from the placenta becomes the dominant lactogenic signal during peak β-cell adaptation. Both PRL and PL exert effects through the prolactin receptor (PRLR), which is expressed specifically on the β-cell of rodent islets [3].

The role of PL in the islet adaptation to pregnancy was initially implicated largely through studies demonstrating that lactogens increased glucose-induced insulin secretion, β-cell proliferation and survival in isolated rodent islets [4–6]. Global homozygous *Prlr* knockout mice exhibit reproductive dysfunction [7], so are unsuitable for pregnant studies. However, heterozygous *Prlr*+/− mice are fertile and have impaired glucose tolerance and reduced β-cell mass during pregnancy [8], but also adipose tissue effects that influence glucose homeostasis. The recently established β-cell specific *Prlr* knockout mouse (βPRLR-KO)provides the best evidence for the role of lactogenic hormones in β-cell adaptation. Although βPRLR-KO mice have normal glucose tolerance outside of pregnancy, they become progressively glucose intolerant during gestation, with corresponding failure of β-cell proliferation [9••].

The intracellular mechanisms activated by lactogenic hormones *in vitro* closely reflect pregnant changes, including glucokinase upregulation [10] and pro-proliferative and anti-apoptotic signalling pathways [11,12]. The lactogenic hormones also stimulate β-cell production of serotonin during pregnancy [13], which appears to play a critical local role in regulating β-cell mass [14], mediating the effects of prolactin (Table 1).

Given the role for lactogenic hormones in rodent pregnancy, there is ongoing research to determine whether similar mechanisms are also relevant in human β-cells. Human PLs are derived from duplications of the *hGH* gene, whilst rodent PLs are evolved from the prolactin gene [15], and the *Prlr* gene is significantly enriched in mouse β-cells compared to human, perhaps indicating a lesser role in human β-cell adaptation [16,17]. Treatment of human islets with lactogenic hormones potentiates glucose-stimulated insulin secretion [18], but the effects on β-cell proliferation are more controversial. Increased proliferation, as assessed by BrdU incorporation, has been reported in human islets in response to PL and PRL [18], but more recent studies have been unable to replicate this effect [19].

It is also unclear whether serum PRL or PL associates with GDM pathophysiology. Several studies have investigated possible links, but the majority found no significant correlation between maternal PRL or PL and GDM [20], although counter-intuitively an association between high maternal prolactin and reduced glucose tolerance has recently been reported [21••]. Despite the apparent lack of association to GDM risk, low PRL or PL levels have been associated with reduced glucose tolerance post-partum and an increased risk of subsequent pre-diabetes/diabetes [22•], suggesting that the lactogenic hormones do play some role in human pregnancy.

Hepatocyte growth factor

Hepatocyte growth factor (HGF), acting via the c-Met receptor, has also been implicated in the islet adaptation to pregnancy. Normally HGF is released from endothelial cells in the islet vasculature to exert local effects on the β-cells [23], however during pregnancy high levels of