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Adiponectin's Role during Pregnancy and Gestational Diabetes

Vernon Gruber*

Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Canada

Introduction

Pregnancy necessitates a number of metabolic adaptations in order to provide adequate energy for foetal growth and development. Gestational diabetes is defined as hyperglycemia that appears during pregnancy for the first time. GDM is a known risk factor for both pregnancy complications and long-term maternal and offspring risk of developing cardiometabolic disease. While pregnancy alters maternal metabolism, GDM can be viewed as a maladaptation to pregnancy by maternal systems, which may include mechanisms such as insufficient insulin secretion, dysregulated hepatic glucose output, mitochondrial dysfunction, and lipotoxicity. Adiponectin is an adipokine derived from adipose tissue that circulates in the body and regulates a variety of physiologic mechanisms such as energy metabolism and insulin sensitivity. Circulating adiponectin levels decrease with insulin sensitivity in pregnant women, and adiponectin levels are low in GDM.

Description

The current state of knowledge about the role of adiponectin and its intracellular signalling pathways in metabolic adaptations to pregnancy. We chose to focus this review on recent studies using pregnant female adiponectin knockout mice, showing several metabolic features of GDM, suggesting that adiponectin deficiency may play a role in GDM development, because clinical evidence has shown a correlation between low circulating adiponectin levels and gestational diabetes mellitus. We also look at additional mouse studies to see how increasing adiponectin levels during pregnancy affects insulin sensitivity and could be used to treat GDM. Several adaptations are required in mammals to sustain pregnancy. For example, the maternal system has increased blood volume and cardiac output, which is accompanied by an increase in renal activity.

To adequately adapt to maternal and foetal needs during gestation, many hormonal, metabolic, and immunological changes, including insulin resistance, are set in motion. Human placental growth hormone (hPGH) levels rise gradually throughout pregnancy, reducing signalling via the insulin receptor substrate-1 (IRS-1) and glucose transporter (GLUT)-4-mediated glucose uptake. Maternal metabolism shifts to a catabolic phase later in pregnancy, lipids increase transiently, and mild hyperinsulinemia occurs. Despite these changes, normoglycemia is maintained and, in some cases, decreases in most pregnancies, which could be due to the dilution effect as blood volume increases in the maternal system. Furthermore, increased insulin production and secretion by the maternal pancreas contribute to maternal glycemia maintenance.

***Address for Correspondence:** Vernon Gruber, Department of Pharmacology and Therapeutics, University of Manitoba, Winnipeg, Canada, E-mail: vernongruber@gmail.com*

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Changes in circulating hormones and cytokines during pregnancy affect insulin tolerance of peripheral tissues as well as compensatory adaptations of pancreatic -cells such as increased proliferation, decreased apoptosis, and increased glucose-stimulated insulin secretion. Progesterone levels rise in the third trimester and may play a role in increasing adipose tissue lipolysis while decreasing insulin sensitivity and glucose uptake in peripheral tissues, including adipose tissue. Increased adipose tissue lipolysis may result in increased fatty acid uptake by the liver and decreased hepatic insulin sensitivity. Human placental growth hormone (hPGH) levels rise significantly during pregnancy and play a role in promoting pregnancy-induced -cell adaptations. Prolactin (PrL) and placental lactogen (PL) have been linked to -cell adaptations during pregnancy, as well as peripheral insulin resistance and increased lipolysis.

Tumour necrosis factor (TNF)- rises in the bloodstream near the end of pregnancy and has been shown to mediate the insulin resistance that occurs in the third trimester. GDM causes more severe insulin resistance, as well as increased inflammation and lipotoxicity, all of which impair pancreatic cell adaptations. Furthermore, impaired insulin sensitivity in the liver results in increased hepatic glucose output and decreased oxidation. Adipose tissue lipid spillover can cause hepatic fat deposition and lipotoxicity in both the pancreas and the liver due to impaired expandability.

The pancreatic islet adapts to pregnancy demands through a variety of adaptive mechanisms, including -cell hyperplasia and hyper-functionality, which are regulated by transcription factors and cell cycle regulators. Pregnancy-induced -cell expansion is accomplished through proliferation, hypertrophic expansion, and possibly neogenesis from progenitor cells; these mechanisms are accompanied by a temporary reduction in apoptosis, which has also been observed in human pregnancy islets. These changes could be mediated by crosstalk between increased placental signalling, the maternal pancreas, and peripheral tissues, as evidenced by animal models. While some adaptive mechanisms are shared by all species, there are differences in the primary adaptive responses of rodent and human islets during pregnancy.

Human islets isolated during pregnancy, on the other hand, are scarce, and the samples were heterogeneous in origin (from pregnancies of varying gestational length, maternal ages, ethnicities, and causes of death), complicating interpretation. Despite the diversity of available samples, human islets isolated during pregnancy show an increase in -cell area when compared to non-pregnant controls. Pregnancy increases alpha-cell mass, pancreatic glucagon-like peptide, and pancreatic and circulating glucagon levels in mice, as well as a transient increase in serum glucagon, as has been previously reported in human pregnancy. Furthermore, pregnant mice lacking -cells were found to have impaired glucose tolerance, which was reversed by the administration of glucagon-like peptide (GLP)-1 receptor agonists, indicating a role for -cells in insulin secretion and islet adaptation to pregnancy [1-5].

Conclusion

Because of issues with protein heterogeneity, solubility, and post-translational modifications, the use of adiponectin as a therapeutic has been largely ruled out. AdipoRon is an orally administered small-molecule adiponectin receptor agonist that has been shown to improve glucose homeostasis, insulin resistance, and dyslipidemia in db/db mice. AdipoRon also protected the hearts of db/db mice from lipotoxicity. AdipoRon reduced hyperglycemia in dams with GDM and improved long-term glucose tolerance in the offspring of

pregnant streptozotocin-induced diabetes treated with AdipoRon, according to a study published in 2021. While Gazquez et alexperiments .'s with AdipoRon in pregnant diabetic rats are an excellent starting point, this model involves -cell destruction to induce hyperglycemia, representing a type 1 diabetes model of diabetes in pregnancy.

While the effects of adiponectin on skeletal muscle metabolism and insulin sensitivity are well established, the effects of adiponectin on skeletal muscle during pregnancy have not been investigated. Furthermore, the insulin-sensitizing properties of adiponectin supplementation in pregnant women remain to be investigated; however, challenges regarding administration and dosages would need to be resolved in order to achieve a successful clinical trial. Adiponectin therapy may also be beneficial in the immediate postnatal period to slow the progression of GDM to T2D in women. Further research into molecules that stimulate adiponectin signalling, such as AdipoRon, during pregnancy could be a more successful approach in this regard.

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