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THE ROLE OF ADIPONECTIN IN HUMAN PREGNANCY

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ABSTRACT

Adiponectin is a macromolecular complex similar to the members of the C1q and other collagenous homologues. Pregnancy is a unique physiologic state that is associate with profound alterations in maternal metabolic, endocrine and vascular function, designed to ensure the delivery of appropriate energy, the role of the fat-derived hormone. Adiponectin is emerging recognition of the broad array of physiologic processes upon which this adipokine impacts. Adiponectin is secreted by white adipose tissue and it is anti-diabetes, anti-atherosclerosis, anti-inflammation and antitumor activities, which directly link to the high molecular weight. Adiponectin mediates its actions in the periphery via two receptors, AdipoR1 and AdipoR2. Adiponectin receptors are present in many reproductive tissues including the central nervous system, ovaries, oviduct, endometrium and testes. Adiponectin influences gonadotropin release, normal pregnancy and assist reproduction outcomes. Adiponectin, a beneficial adipokine, represents a major link between obesity and reproduction. Higher levels of adiponectin are associate with improve menstrual function and better outcomes in assisted reproductive cycles.

KEYWORDS: Adiponectin, Adiponectin Receptors, Obesity, Reproduction, Placenta, Pregnancy

INTRODUCTION

Obesity reach epidemic proportions in developing and developed countries. Obesity is the most common chronic disease in the U.S. According to the practice committee of the American Society for Reproductive Medicine [1]. Despite worldwide awareness, incidence of obesity is increasing and obesity describe as the new worldwide epidemic [2]. Metabolic disorders such as the development of insulin resistance result from the increasing incidence of obesity and have serious ramifications on the progression of lifetime health problems such as type II diabetes, cardiovascular disease, dyslipidemia and hypertension.

Adipose tissue secretes proteins and lipids and metabolizes hormones that regulate not only energy homeostasis but also influence reproduction and immune function. A significant proportion of the infertile population are obese with a plethora of reproductive complications including menstrual dysfunction and an ovulation, and miscarriage [3,4,5,6,7,8,9,10].

Adipose tissue secretes several proteins and bioactive peptides adipokines that act either locally [11]. Adipose tissue is primarily compose of lipid laden adipocytes surrounded by loose connective tissue. In humans, most fat is white adipose tissue, in contrast to animals, which is brown adipose tissue [12]. The abundant adipocytes serve as triglyceride storage and are surrounded by a network of collagen fibers, vascular elements, fibroblasts and immune system cells [12]. The metabolic role of adipose tissue is an energy storage compartment. Many of the metabolic consequences of obesity are cause by altered secretion of adipokines.

Adipose tissue functions as a highly specialized, endocrine and paracrine organ producing an array of adipokines, as well as eliciting cell mediate effects via proinflammatory and anti-inflammatory cells and also producing various cytokines and chemokines. Such factors have local and systemic biological effects, influence insulin sensitivity and the development of diseases such as atherosclerosis.

ADIPONECTIN

Adiponectin independently discovered between 1995 and 1996 and given different names including apM1, Acrp30, GBP28 and adipQ [13,14].

Adiponectin is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism and secreted from adipose tissue into the blood-stream and is very abundant in plasma relative to many hormones[15]. The adiponectin gene is located on chromosome 3q27, in a region as a susceptibility locus for type II diabetes and adiposity and is thought to potentially link obesity to insulin resistance[16,17,18].

Adiponectin is a protein of 245 amino acids, consisting of four domains, an amino-terminal signal sequence, a variable region, a collagenous domain (cAd)and a carboxy-terminal globular domain (gAd)[14].

Adiponectin is one of the most abundantly secreted adipokines and corresponds to 0.05% of the serum proteins [20]. The serum levels are 3–30 mg/mL in humans and 3–6 mg/mL in rodents [21]. Adiponectin is related to the complement 1q family and contains a carboxyl-terminal globular domain and an aminoterminal collagenous domain. Adiponectin secrete by adipose tissue in the form of a trimer as a low-molecular-weight (LMW), a combination of two trimers as a middle molecular weight (MMW) or as six trimers as a high-molecular-weight (HMW) form and circulates either as a trimer or an oligomer [22,23,24,25].

Adiponectin cDNA was first isolated by large scale random sequencing of the human adipose tissue cDNA library. It is a collagen like protein that is exclusively synthesized in white adipose tissue and is induce during adipocyte differentiation and circulates at relatively high concentrations in the serum. Once synthesized, mammalian adiponectin undergoes post-translational, hydroxylation and glycosylation yielding eight isoforms. Six of the adiponectin isoforms are glycosylated[26].

Receptors for adiponectin, AdipoR1 and AdipoR2 discovered in mice and a third receptor, t-cadherin identified although the tissue distribution and functional significance of the latter remain to be elucidate [27,28].

Actions of adiponectin mediated through activation of AMPK, leading to inhibition of acetyl coenzyme A carboxylase and an increased fatty acid beta-oxidation [29]. Activation of AMPK acts to regulate energy homeostasis of the cell via fatty acid oxidation and glucose uptake stimulation. Adiponectin is markedly reduce in obesity and rises with prolong fasting and severe weight reduction.

AdipoR1 express ubiquitously, most abundantly in skeletal muscle, whereas AdipoR2 express in the liver. AdipoR1 functions as a high affinity receptor for globular adiponectin and a low affinity for full length adiponectin[30].

Adiponectin suppresses SREBP1c by AdipoR1, one of the functional receptors for adiponectin, and furthermore that suppressing either AMP-activated protein kinase (AMPK) via its upstream kinase LKB1 deletion cancels the negative effect of adiponectin on SREBP1c expression[31].

Both AdipoR1 and AdiopR2 bind adiponectin with an EC50 in the range of 0.7–2.4 pmol/L [32].

In addition to its effects on insulin sensitivity, adiponectin increases lipoprotein lipase and lowers lipid levels, increases nitric oxide production in endothelial cells and induces angiogenesis and mediates anti-inflammatory and antiatherogenic actions [33,34,35,36,37]. It is reported, the adiponectin levels are low in patients with breast cancer, endometrial cancer, gastrointestinal cancer and prostate cancer [38,39,40,41,42].

Moreover, adiponectin acts as a hormone to fine-tune energy homeostasis involving food intake and the catabolism of carbohydrate and lipid and may offer an interesting alternative treatment for type II diabetes, obesity and metabolic disturbances [2,43].

ADIPONECTIN AND PREGNANCY

Pregnancy is a unique physiologic state that is associated with profound alterations in maternal metabolic, endocrine and vascular function, and designed to ensure the delivery of appropriate energy and nutrition to the developing fetus. In this context, the role of the fat derived hormone adiponectin is emerging recognition of the broad array of physiologic processes upon which this adipokine impacts.

The effects of adipokines on the process of ovulation, ovarian steroidogenesis and the maintenance of pregnancy have received limited attention. A role of adiponectin in ovarian steroidogenesis described but an interaction is likely given the negative effects of testosterone on circulating adiponectin in humans [49,50].

Cytokines produce by three different placental cell types; the Hofbauer cells, the trophoblast cells and the vascular endothelium cells. Adiponectin receptors are present in the human placenta. The human placenta express adiponectin. AdipoR2 particularly expressed in human syncytiotrophoblast and cytotrophoblast [50,51,52,53]. Placental adiponectin acts through a pathway common for adiponectin by altering the phosphorylation status of p38 and MAPK [51].

Adiponectin has a direct role to obesity or gestational diabetes but recent finding suggest that a role for adiponectin and AdipoR1 in placental angiogenesis and placental apoptosis. Recent data also shows which adiponectin secretion and adiponectin transcript levels in white adipose tissues decline as gestation progress even in lean women [54,55,56,57,58]. Adiponectin is reduced by increasing concentrations of estrogens and increased of hCG [45].

Adiponectin is implicate in the pathogenesis of insulin resistant and increase in adiponectin levels promotes insulin sensitivity. The beginning of pregnancy is characterize by tissue accretion where as late pregnancy is notable for insulin resistance and facilitate lipolysis. In early pregnancy, insulin secretion increases, although insulin sensitivity is unchanged, decreased or even increased. In late gestation, because of the progressive increase in postprandial glucose, insulin requirements must increase [43,46,47].

Adiponectin is negatively correlated with HOMA-IR and a decrease in maternal adiponectin after delivery indicates a significant placental contribution to adiponectin production. In addition, adiponectin levels correlate with whole body insulin sensitivity, because of the insulin sensitizing effects of adiponectin in muscle and liver, adiponectin reduces hepatic glucose production and enhances insulin action in the liver and peripheral utilization of glucose[19,48]. Given these data regarding expression of AdipoR1 and AdipoR2 in the placenta, adiponectin may affect the constantly changing metabolic state throughout pregnancy.

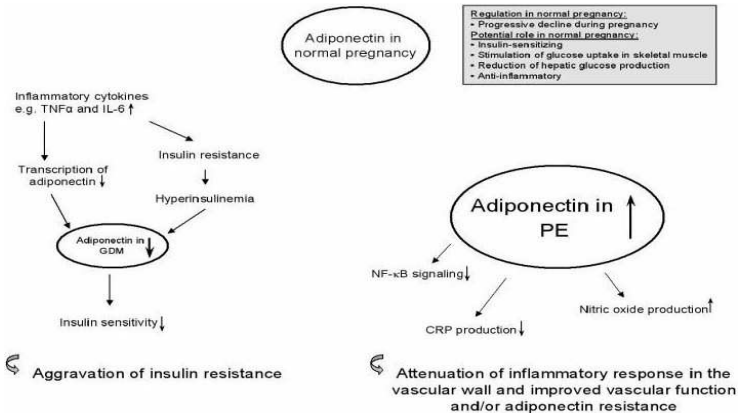

Figure 1

CONCLUSIONS

The adiponectin produced by adipose tissue and altered with obesity, clearly influence energy homeostasis and undoubtedly affect female fertility. The paucity of information implicating a role for adiponectin at any central of female reproduction makes any firm statements at this time precarious in nature.

Obesity is causing serious health issues, including anovulation and infertility. Because it is associate with low adiponectin levels and given that many reproductive endocrine tissues express adiponectin receptors, adiponectin represents an important hormonal link between adipose tissue and the reproductive system. The relationship between obesity and normal endocrine reproductive function is fertile ground for future research.

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