Do novel adipokines play a causative or only modulating role in the pathogenesis of obesity and metabolic disorders?

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Abstract
Adipose tissue is an endocrine and paracrine organ that releases a large number of bioactive mediators. Approximately 100 adipokines have been identified including cytokines, chemokines, growth factors and enzymes. The use of adipoproteomic analyses resulted in new findings and, in consequence, the number of new adipokines is rising rapidly. Novel adipokines such as visfatin, vaspin and omentin were discovered about five years ago. Visfatin and vaspin production and secretion take place in adipocytes, but omentin comes from the stromal cells of adipose tissue. Several differences are noticeable between these adipokines especially in correlation with obesity as visfatin and vaspin serum levels increase in obese subjects while omentin serum levels decrease. It has been suggested that these adipokines act as insulin-sensitizers/insulin-mimetics. Increasing number of publications reporting the role of new adipokines does not allow to assess clearly the influence of those adipokines on the pathogenesis of obesity.

INTRODUCTION
Obesity, characterized by excessive accumulation of adipose tissue, is caused by an imbalance between energy intake and expenditure. It is a rapidly growing disease affecting about 300 million people worldwide. Several factors are thought to contribute to fat excess including genetic factors and their interaction with multiple environmental components. Obesity is associated with a wide range of health consequences like insulin resistance, type 2 diabetes mellitus (T2D), hypertension, hyperlipidemia and atherosclerosis.

Adipose tissue consists of white (WAT) and brown adipose tissue (BAT). In general, BAT is responsible for thermogenesis. It makes about 25% of neonate body mass and reduces in adults. WAT creates the greatest part of adipose store being divided into two large depots: subcutaneous and visceral, and many small depots associated with internal organs such as heart, blood vessels, major lymph nodes, pancreas, prostate gland and ovaries. The omental visceral fat in comparison to subcutaneous one is more metabolically active and also contains much more amount of insulin-resistant adipocytes (Johnson et al. 2001; Sharma 2002). Body fat distribution is of a great importance because visceral obesity is associated with higher risk of insulin resistance, type 2 diabetes and cardiovascular disease in comparison to subcutaneous type of obesity (Björntorp 1991). Growing amount of visceral adiposity enhances an increase of circulating non-esterified fatty acid (NEFA) levels. In result, insulin plasma levels elevate and then inhibit glucose absorption of insulin-sensitive tissue such as liver or muscles. This long-term
inhibition may contribute to insulin resistance. Moreover, it has been suggested that increased NEFA circulating levels could inhibit activity of glucose transport (Felber et al. 2002; Sharma 2002).

Adipose tissue is composed of adipocytes embedded in a matrix of connective tissue, fibroblasts, endothelial cells and immune cells like monocytes and macrophages (Sharma 2002). Adipose tissue has been considered as an active endocrine organ from the time of leptin discovery in 1995 (Trujillo et al. 2006). Since then, a large number of bioactive mediators produced by adipose tissue, collectively named adipokines, have been isolated (Renes et al. 2009; Poulos et al. 2010). These substances such as adiponectin, leptin, resistin, visfatin, vaspin, omentin, tumour necrosis factor (TNF-α) and interleukin-6 (IL-6) have a wide variety of biological functions including modulation of lipid and glucose metabolism, blood pressure or inflammation (Rabe et al. 2008).

**VISFATIN**

Visfatin was isolated in 2005 and described as an adipokine with insulin mimetic effects that directly binds to and then stimulates the insulin receptor (Fukuhara et al. 2005). It was named “visfatin” to underline that it is preferentially expressed in abdominal visceral fat (Fukuhara et al. 2005, Pagano et al. 2006). Visfatin had been originally identified about ten years earlier, as a pre-B cell colony enhancing factor (PBEF), cytokine produced by lymphocytes which enhanced the effect of IL-7. PBEF was then characterized as protein being produced by lymphocytes which enhanced the effect of IL-7. PBEF was then characterized as protein being produced by lymphocytes which enhanced the effect of IL-7. PBEF was then characterized as protein being produced by lymphocytes which enhanced the effect of IL-7. PBEF was then characterized as protein being produced by lymphocytes which enhanced the effect of IL-7. 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concentrations in obese patients in whom visfatin levels decreased after weight loss. However, another studies showed reduced plasma visfatin levels in obese animals and humans (Pagano et al. 2006; Mercader et al. 2008). The presented data suggest that regulation of visfatin production under conditions of obesity is not entirely clear.

Aside from the fact that visfatin is an adipocyte-specific protein, this protein has been also considered as an inflammatory cytokine being produced and released by the macrophages of adipose tissue (Curat et al. 2006). Addition of recombinant visfatin could increase, in the dose-dependent manner, the production of the pro- and anti-inflammatory cytokines such as IL-1, IL-6, IL-10 and TNF-α in human monocytes (Moschen et al. 2007). Visfatin association with IL-6 seems to be one of the most significant amongst adipokines (Oki et al. 2007). It has been reported that visfatin acts as a mediator of inflammation which induced the production of IL-6 in human monocytes by MAPK and MAPK kinase 1 (MEK1) pathways (Moschen et al. 2007). Visfatin produced by neutrophils, macrophages and monocytes remains up-regulated in many acute inflammatory diseases such as acute lung injury (Ye et al. 2005), inflammatory bowel disease (Moschen et al. 2007) and rheumatoid arthritis (Otero et al. 2006).

It has also been reported that visfatin is able to induce oxidative stress by generating reactive oxygen species (ROS). The NfκB pathway is involved in this particular effect (Oita et al. 2010).

**VASPIN**

A novel adipokine vaspin has been identified for the first time in visceral white adipose tissue (WAT) of Otsuka Long-Evans Tokushima Fatty (OLETF) rats (animal model of type 2 diabetes, characterized by abdominal obesity, dyslipidemia, insulin resistance and hypertension) (Hida et al. 2005). After identification and characterization as a new member of serpin (serine protease inhibitor) family it was named “vaspin” (visceral adipose tissue-derived serpin). It is worth noticing that although it has reactive site loop and shows structural homology to serpin, its serine protease inhibitor activity has not been observed yet.

Vaspin gene expression increases in 30-week old OLETF rats when obesity and insulin resistance develop, however decreases in 50-week old OLETF rats with worsening of diabetes and body weight loss (Hida et al. 2005). Hida et al. (2005) demonstrated that vaspin mRNA expression is induced by addition of insulin or thiazolidinedione to this rat, which suggest that vaspin could play a role in compensation for the impairment of glucose metabolism and insulin sensitivity. Moreover, these authors found that administration of recombinant human vaspin to mice with diet-induced obesity results in significant improvement of both insulin sensitivity and glucose tolerance. In addition, vaspin also influences the expression of genes involved in the pathogenesis of insulin resistance such as genes of resistin, leptin, adiponectin, glucose transporter-4 and TNF-α (Hida et al. 2005).

Human vaspin is composed of 395 amino acids and it is homologous in 40% to alpha 1-antitrypsin, acute-phase protein originated from the liver, which level increases during inflammation (Gettins 2002). Human vaspin is expressed in visceral and subcutaneous adipose tissue in obese people with normal glucose tolerance (NGT) but it is not detected in WAT of lean subjects with NGT (Klöting et al. 2006). It seems that vaspin gene expression is regulated depending on the fat depot. Visceral vaspin expression is found to be significantly correlated with BMI, percentage of body fat and serum glucose levels following 2 hrs oral glucose tolerance test (OGTT). On the other side, subcutaneous expression of vaspin gene is significantly correlated with waist-to-hip ratio (WHR), fasting plasma insulin concentration and glucose infusion rate during steady state of the euglycemic–hyperinsulinemic clamp (Klöting et al. 2006). Vaspin serum concentrations are correlated with obesity. Its elevated levels impair insulin sensitivity, however, this correlation is not observed in patients with type 2 diabetes (Youn et al. 2008; Handisurya et al. 2010). It is possible that metformin used in the type 2 diabetes treatment decreases serum vaspin levels via glucose-lowering effect by suppression of hepatic glucose production (Johnson et al. 1993; Inzucchi et al. 1998). Interestingly, low serum vaspin concentrations are found in subjects with long-term physical training activity, although elevated values of this peptide are observed during the first 4 weeks of intensive exercise training (Youn et al. 2008). Interpretation of this paradox considers hypothesis that vaspin regulation differs dependently on the resting state and after exercise. Besides, differences in serum vaspin levels are also observed between patients with or without microvascular complications as those with microvascular changes have lower values (Gulcelik et al. 2009).

Similarly to other adipokines, leptin and adiponectin, vaspin serum concentrations are gender-dependent and are found to be significantly higher in female than male subjects (Youn et al. 2008). This difference might be a result of the amount of adipose tissue and its distribution. Interestingly, in type 2 diabetic patients this gender-dependent dissimilarity is absent. It seems that hyperglycemia or decreased insulin sensitivity could modulate vaspin levels. Besides, the comparison of serum vaspin concentrations between premenopausal and postmenopausal women did not demonstrate significant differences and thus, it could be suggested that estrogens do not participate in the regulation of vaspin (Handisurya et al. 2010).

In addition, the initial studies indicated that vaspin might also reveal anti-inflammatory effects as it is able to suppress leptin, TNF-α and resistin expression (Hida et al. 2005).
OMENTIN

In 2005 Yang et al. (2006) identified a new adipokine, named omentin, which is highly expressed in visceral omental adipose tissue but barely identifiable in subcutaneous fat depots. Omentin is not secreted by adipocytes but it is primarily expressed in adipose stromal vascular cells (SVCs) in humans (Schäffler et al. 2005; Yang et al. 2006). Moreover, low expression of omentin is found in other tissues and is named intelectin (Tsujii et al. 2001), intestinal lactoferrin receptor (Suzuki et al. 2001) and endothelial lectin (Lee et al. 2001).

The two omentin genes are localized in adjacent regions of chromosome and encode 2 highly homolog isoforms. The omentin-1 gene, encodes 34 kDa protein with 313 amino acids. It is located on chromosome 1q21.3 and consists of 8 exons and 7 introns (Schäffler et al. 2005). Omentin-1 is the main isoform in human plasma.

Decreased level of omentin-1 is observed in patients with type 1 diabetes mellitus (De Souza Batista et al. 2007), type 2 diabetes (Pan et al. 2010) and in those with impaired glucose regulation (Pan et al. 2010). It has been demonstrated that omentin-1 improves insulin action by increasing insulin-stimulated glucose uptake by subcutaneous and omental adipocytes in vitro (Yang et al. 2006). Furthermore, omentin-1 induces Akt signaling independently of the absence or presence of insulin (Schäffler et al. 2005; De Souza Batista et al. 2007). In contrast, in cultured adipocytes omentin-1 expression and its circulating levels are negatively correlated to D-glucose and insulin concentration (De Souza Batista et al. 2007). Moreover, decreased plasma levels of omentin and suppressed gene expression are found in visceral adipose tissue in a course of obesity (De Souza Batista et al. 2007). In lean women higher circulating level of omentin-1 are found when compared to those in men, whereas less noticeable gender-dependent differences in omentin values are observed in overweight and obesity. Omentin-1 plasma estimation negatively correlates with leptin levels, BMI and homeostasis model assessment (HOMA), and positively with adiponectin and high-density lipoprotein (HDL) levels (De Souza Batista et al. 2007; Moreno-Navarrete et al. 2010).

CONCLUDING REMARKS

Since the discovery of leptin nearly 15 years ago it has been allowed to consider an adipose tissue as endocrine organ. Recent identification of novel adipokines has broadened the spectrum of research. As the results of the studies are ambiguous, our knowledge of novel adipokines role in obesity and metabolic diseases is also not complete. Further intensive investigations are needed to answer the question whether these adipokines play a causative role in the pathogenesis of obesity or they only reflect the metabolic abnormalities. It seems that adipokines may be used as markers and help to determine the group of patients who will develop obesity and metabolic disorders.

REFERENCES


Novel adipokines in obesity and metabolic disorders


