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MINIREVIEW ARTICLE

Visfatin in pregnancy: proposed mechanism of peptide delivery

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Abstract Visfatin is a newly identified 52 kD adipocytokine that appears to have insulinomimetic properties. We examined visfatin expression in visceral fat from lean and pregnant women. Visfatin gene expression was seven times higher in omental fat of pregnant women than in lean women. Both immunohistochemistry and immunoblot confirmed that visfatin protein was much higher in pregnant women than in nonpregnant women. However, serum visfatin was 20.8 ± 7.7 ng/ml ($n = 7$) in lean women as compared to only a slight increase to 40.3 ng/ml in pregnant women ($n = 4$). We measured visfatin mRNA content of human placenta and found that placenta expresses high levels of visfatin mRNA and protein. At a concentration of 2 nM, visfatin and insulin produced nearly identical increase in glucose transport. The discrepancy between the elevated visfatin expression and tissue visfatin compared to only a small increase in serum visfatin is a matter of controversy. The data on serum visfatin concentrations are replete with contradictory data. Taken together, we suggest that visfatin is not a hormone. Instead, we propose that visfatin acts in either a paracrine or autocrine mode. This hypothesis would explain what various laboratories have found widely discrepant values for serum visfatin. Since visfatin potently and efficaciously induced glucose transport in a cell culture model, any hypothetical role for visfatin in pregnancy should include the possibility that it may play a role in maternal/fetal glucose metabolism or distribution and that it may do so by acting locally.

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Introduction

Over the decades, our perception of adipose (fat) tissue has been significantly transformed. It is no longer considered merely a fat reservoir, but is a significant endocrine organ, secreting many different metabolically active compounds including adipokines. Obesity is an increasing problem throughout industrialized countries and becoming a worldwide public health issue for the twenty first century (Berndt et al. 2005). An accumulation of abdominal visceral body fat is the hallmark of obesity and is a substantial risk factor for insulin resistance in type 2 diabetes (Briana et al. 2007). A variety of adipocytokines, including visfatin, secreted from adipocytes may play a crucial role in the development of obesity, metabolic syndrome, insulin resistance, and gestational and type 2 diabetes (Dahl et al. 2007; Zhong et al. 2008; Chen et al. 2006; Chan et. al. 2006; Tilg et al. 2008). Visfatin is a novel adipocytokine that binds the insulin receptor (IR), initiating downstream phosphorylation events and induces glucose transport (Xie et al. 2007; Fukuhara et al. 2005). It is a 52 kD insulinomimetic peptide secreted by visceral fat tissue. It is identical to pre-B cell colony enhancing factor (PBEF, a cytokine), and nicotinamide phosphoribosyltransferase (Nampt, an enzyme) (Sethi and Vidal-Puig 2005; Petraglia et al. 1996). Visfatin is mainly expressed in adipose tissues, with particularly high levels in both visceral and omental adipose tissue. In contrast, subcutaneous adipose tissue expresses little visfatin. Visfatin is expressed in other tissues such as placenta (Morgan et al. 2008; Malamitsi-Puchner et al. 2007; Fasshauer et al. 2007; Kendal-Wright et al. 2008), liver (Fukuhara et al. 2005; Kim el al. 2006), skeletal muscle (Krzysik-Walker et al. 2008; Pilz et al. 2007), fetal membranes (Malamitsi-Puchner et al. 2007) and cardiac tissue epicardial fat (Malavazos et al. 2008;

Cheng et. al. 2008; Fain et al. 2008); however, its physiological activity is yet to be identified.

Visfatin, an insulinomimetic agent

Visfatin has been shown to have insulinomimetic activity (Chan et al. 2006). Fukuhara et. al. (2005) demonstrated that visfatin binds to the IR, induces glucose uptake into adipose tissue and skeletal muscle in both mice and humans. However, this paper has been retracted from Science (Fukuhara et al. 2007). In this study, visfatin does not appear to compete with insulin to bind the IR, suggesting that it may bind to another site at the extracellular binding domain (Fukuhara et al. 2005). Visfatin induces phosphorylation of the IR and IR substrates 1 and 2 in human osteoblasts and in human adipocytes in vitro (Xie et al. 2007; Haider et al. 2006). In addition, Fukuhara et al. (2005) found binding of phosphotidylinositol 3-kinase (PIK3) to IRS-1 and phosphorylation of both Akt and mitogen-activated protein kinase (MAPK), actions that mimic the effects of insulin (Fukuhara et al. 2005). In our recent study (Morgan et al. 2008), we have demonstrated visfatin induced glucose uptake in differentiated adipocytes (NIH 3T3-L1 cells). At concentration of 2 nM, visfatin-induced glucose uptake was comparable to that produced by insulin (Table 1). Thus, visfatin appears to promote glucose transport by mechanisms similar to insulin. GLUT4 translocation in response to visfatin has yet to be demonstrated. However, in our hands 2 nM visfatin does induce movement of the GLUT 4 transporter from its cytosolic store to the membrane in differentiated 3T3-L1 cells (data not presented). Thus, visfatin appears to promote glucose transport by mechanisms similar to insulin. Taken together, these data suggest that insulin and visfatin act in concert to lower blood glucose.

Visfatin in human pregnancy

Gestational diabetes does not receive as much attention as type 1 and 2 diabetes, but is a common complication of pregnancy. Here, we summarize the data on visfatin that suggest it may be involved in pregnancy and gestational diabetes. We have found that the visfatin mRNA transcript and peptide are eight- to ten-fold higher in pregnant than in lean women (Morgan et al. 2008).In addition, we have identified visfatin transcript as well as protein in the human placenta. Histological examination revealed that visfatin distribution was limited exclusively to the villous capillary of the fetal endothelium (Morgan et al. 2008). It is tempting to speculate that given this distribution, visfatin could play a role in the transfer of glucose from maternal to fetal blood.

Maternal obesity and gestational diabetes are common consequences of pregnancy (Kalhan et al. 1997; King 2006; Malamitsi-Puchner et al. 2007). Pregnant women often gain weight during the gestation and it is not uncommon for them to become diabetic/insulin resistant during the third trimester. Therefore, in our recent study (Morgan et al. 2008), two additional control groups, obese women (BMI $>$ 40) and obese diabetic women (BMI $>$ 40) were added. By including these two additional control groups, the data accounted for any changes in weight or diabetic status in pregnant women. In our study (Morgan et al. 2008), we demonstrated that visfatin mRNA expression was seven times higher in omental fat of pregnant women than fat from lean women (Fig. 1). Additionally, neither obese nor obese diabetic women expressed any more visfatin than did lean women. That is the increase in visfatin expression is specific to pregnancy. We have confirmed translation of visfatin into a 53 kDa protein by immunohistochemistry (IHC) and immunoblot. Again, as was observed for the mRNA transcript, visfatin protein levels were much higher in pregnant women than in nonpregnant women. The increased visfatin mRNA/protein expression levels in omental fat were not reflected in increased serum visfatin levels, however. Although visfatin is a secreted peptide; it does not have signal sequence, which is a common hallmark of almost all secreted hormones. The lack of correlation between mRNA transcript and local tissue concentration of peptide lead the authors to conclude that visfatin acts locally in a paracrine or perhaps autocrine mode of action as opposed to a classical blood borne endocrine agent (Fig. 2). In pregnancy, increased adipose tissue is a forerunner of significant progressive increase in insulin resistance and adipose tissue-derived visfatin may act as an insulinomimetic agent, aiding insulin sensitivity during the second and third trimester.

Table 1 Visfatin induces glucose uptake

Group	2-Deoxyglucose uptake (2 nM 2DG/min)
Control	0.6 ± 0.2
2 nM Insulin	4.1 ± 0.5
2 nM Visfatin	4.6 ± 0.3

Serum levels of visfatin

There are contradicting reports on serum levels of visfatin in pregnancy. Recent literature highlight the increased serum levels of visfatin in obese, diabetic, and pregnant

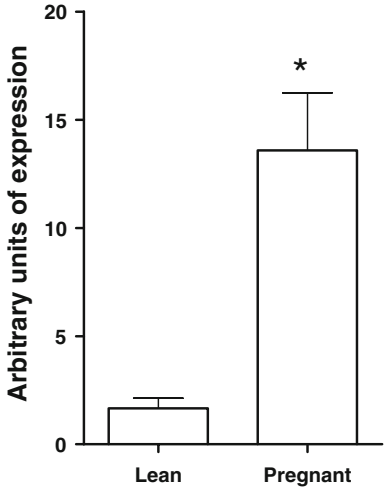

Fig. 1 Visfatin mRNA expression in human omental fat from pregnant and lean women. Data expressed as visfatin expression relative to GAP-DH controls (log 2 transformation of the ΔCt values) using the quantitative real-time RT-PCR. Visfatin expression in pregnant women omental fat was significantly different compared to lean ($*P \leq 0.038$; $n = 7$ in each group)

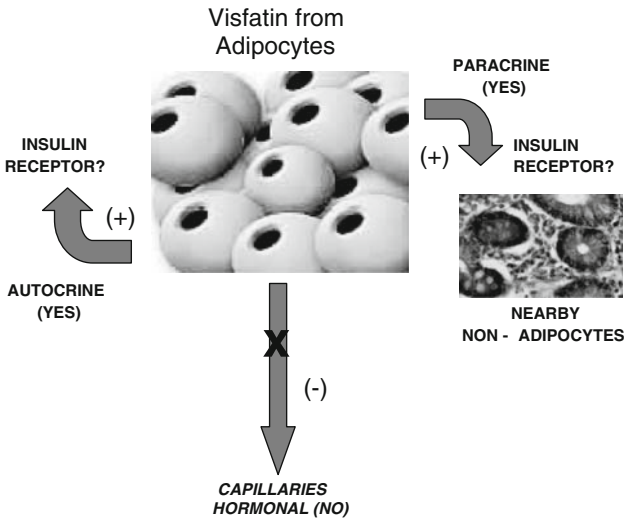

Fig. 2 Proposed mechanism of visfatin delivery. This paper suggests that visfatin is secreted from both adipocytes and placenta but works solely in paracrine and/or autocrine manner. It acts in both of these cells and perhaps surrounding tissues. It does not enter the bloodstream and behave as a circulating hormone. See text for details

patients (Hu et al. 2008; Fasshauer et al. 2008), but a few reports published very recently do not concur with these findings and reported no significant change in the serum visfatin levels in these groups (Morgan et al. 2008). Hu et al. (2008) reported very high levels of human serum visfatin in control nonpregnant women (626 ± 45.5 ng/ml), pregnant women (695.9 ± 92.5 ng/ml) and pregnant women with pre-eclampsia (308.3 ± ng/ml). These serum visfatin levels are 10–20-fold higher compared with various other reports dealing with similar studies in pregnant women (in the range of 9.4–40 ng/ml) (Chan et al. 2006; Fasshauer et al. 2008; Morgan et al. 2008; Malamitsi-puchner et al. 2007). Also, there are contradicting reports on serum/plasma visfatin concentrations in pregnant women with gestational diabetes mellitus. Krzyzanowska et al. (2006) report elevated serum visfatin levels in pregnant women with gestational diabetes mellitus compared with control, which increased during the course of pregnancy as well as after delivery. However, Chan et al. (2006) reported significantly lower levels of plasma visfatin concentrations in the gestational diabetes mellitus group than in the healthy control group of pregnant women (9.4 ± 3.8 vs. 12.6 ± 4.5 ng/ml). Morgan (2008) et al.'s suggestion that visfatin acts in a paracrine or autocrine mode of action would explain why there are discrepancies in reports of circulating visfatin in pregnancy. If visfatin acts only locally then measuring circulating blood levels would be ineffective (Fig. 2). None of these studies establish any meaningful correlation between the serum levels of visfatin and pregnancy or complications of pregnancy.

Conclusion

Visfatin is a newly discovered adipocytokine secreted by adipose tissue (adipocytes), which may facilitate insulnimimetic activity in pregnancy and gestational diabetes. This makes it a very attractive small molecule target for the treatment of insulin resistance in type 2 diabetics. However, the exact local autocrine/paracrine mechanisms of visfatin exerting insulin-mimicking effects that improve insulin sensitivity and its role in human pregnancy are still unclear. Its transcription and translation are highly elevated in pregnant women as compared to obese, obese diabetic and lean women. It is also expressed in human placenta. There are huge discrepancies in reports of circulating visfatin in pregnancy due to large variations in serum visfatin data; further investigation is required with larger numbers of pregnant women.

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