Does visceral fat produce insulin?

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Obesity is associated with an increased risk for the development of type 2 diabetes mellitus (1). Work from the last 15 years has revealed that adipose tissue serves as an endocrine organ, producing a variety of factors that may favour the development of insulin resistance and type 2 diabetes mellitus or protect against its genesis (2). Among these secreted factors are leptin, adiponectin, resistin, tumor necrosis factor and others that have been shown to be involved into the pathogenesis of type 2 diabetes mellitus (3). A brief overview of factors synthesised by adipose tissue, liver and leucocytes is pictured in Figure 1. However, insulin production is conferred strictly to the pancreas. Hyperinsulinaemia is a physiological attempt by the organism to compensate the ever-increasing state of insulin resistance. Therefore, the production of an insulin-mimetic in human adipose tissue might possibly lengthen the phase until hyperinsulinaemia meets with type 2 diabetes.

Fukuhara and co-workers (4) have now introduced a new adipokine derived predominantly from visceral adipose tissue, functioning as an insulin-mimetic in various tissues and organs. Using the differential display of gene expression in adipose tissue, visfatin was detected in visceral adipose tissue and to a much lower extent in subcutaneous adipose tissue. Going in line with that, its plasma concentration was closely related to the amount of visceral fat mass in mice and humans. Therefore, the authors named their newly discovered substance visfatin. Surprisingly, this protein shares 100% homology with a factor with substantial importance for early B-cell development (B-cell colony-enhancing factor, PBEF) (5). PBEF was later identified as an enzyme with a nicotinamide phosphoribosyl-transferase activity localized in both the nucleus and cytoplasm. In addition, it seems that PBEF is released by destruction of the cells rather than by active secretion (6, 7).

Injecting KKAy mice (obese mice used as a model of type 2 diabetes) with recombinant visfatin exerted a glucose-lowering effect on these animals. The fact that plasma insulin levels were unaffected in these animals implied that visfatin acts independent of insulin. Chronic adenovirus-mediated overexpression of visfatin in mice led to a slight but persistent decrease in glucose and insulin concentrations in these animals. A heterozygous disruption of the visfatin gene in mice resulted in elevated plasma glucose concentrations and defective glucose tolerance (animals that are homozygous for this deletion die in utero). Fukuhara and co-workers (4) demonstrated that visfatin uses a system of tyrosine phosphorylation-dependent signalling comparable to

Figure 1 Role of adipose tissue, liver and leucocytes in the contribution of beneficial or deleterious effects regarding the regulation of insulin sensitivity (modified according to (1–3, 10). Adipose tissue produces all of the annotated proteins; liver and leucocytes contribute only to the secretion of some of these hormones/cytokines. TNF, tumor necrosis factor; IL-6, interleukin-6; PAI-1, plasminogen-activator inhibitor 1; MCP, monocyte chemoattractant protein.
that of the insulin receptor. Visfatin and insulin shared an equal binding affinity for the insulin receptor. However, visfatin did not compete with insulin, leading to the suggestion that the two hormones may use two different binding sites on the insulin receptor.

Despite the exciting discovery of an insulin analogue that is synthesized by visceral fat its exact contribution to the actual lowering of plasma glucose concentrations remains rather uncertain if not disappointing: First, Fukuhara and co-workers (4) demonstrated that plasma visfatin concentration did not change significantly upon fasting or feeding, as is known for insulin. This limits the role of visfatin in regulating glucose concentrations in the acute situation. Second, the absolute concentrations of visfatin in mice were 10–30-fold lower than those of insulin.

Nonetheless, the most interesting description of the visceral fat-derived insulin-mimetic visfatin might become a useful target for future drug therapies of diabetes mellitus. First, in vitro studies in 3T3-L1 adipocytes have already demonstrated a positive regulatory effect of dexamethasone on visfatin mRNA concentration, whereas growth hormone, tumor necrosis factor α, interleukin-6 and isoproterenol appear to downregulate visfatin expression (8, 9).

In summary, the discovery of visfatin increases the evidence for adipose tissue working as an endocrine organ, by producing a hormone with a direct insulin-mimetic effect.

References


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Received 29 June 2005
Accepted 6 July 2005