Adipose Tissue is an Endocrine Gland Secreting Multiple Hormones

You Are What You Secrete is a summary and editorial by Saltiel in which he discusses two articles concerning adiponectin.[1] Saltiel emphasizes that our notion of the adipocyte as merely a cargo space for fat has undergone a dramatic change. We now know that adipose tissue is much more complex than previously thought, secreting proteins which include tumor necrosis factor (TNF)-α, leptin, adipsin, resistin and adiponectin known also as Acrp30 or adipoQ. These proteins perform diverse functions but share structural properties of cytokines, and are referred to collectively as "*adipokines*". Dynamic interactions occur between these proteins and dictate the extent to which insulin is sensed in its target tissues. In an article referred to by Saltiel, Berg et al[2] report that a single injection of adiponectin leads to a 2-3 fold elevation in its circulating levels, which precipitates a transient decrease in basal glucose levels. Similar treatment in ob/ob or streptozotocin - treated mice transiently abolishes hyperglycemia. This relative hypoglycemic effect is not associated with an increase in insulin levels. Moreover, in isolated hepatocytes adiponectin increases the ability of sub-physiological levels of insulin to suppress glucose production. Berg et al propose that adiponectin is a potent insulin enhancer linking adipose tissue and whole body glucose metabolism.

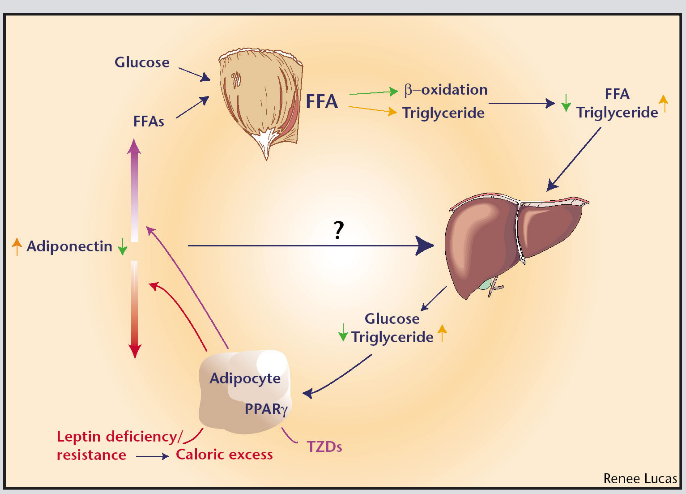
In the article by Yamauchi et al[3] the reversal by adiponectin of insulin resistance associated with both lipoatrophy and obesity is described. Yamauchi et al discuss the findings that recent genome-wide scans have mapped a susceptibility locus for type 2 diabetes to chromosome 3q27, where the gene encoding adiponectin is located. This group demonstrated decreased expression of adiponectin and its correlation with insulin resistance in mice models of altered insulin sensitivity. Adiponectin decreases insulin resistance in obese mice by decreasing triglyceride content in muscle and liver. Insulin resistance in lipoatrophic mice was completely reversed by the combination of physiological doses of adiponectin and leptin, but only partially by either given alone. Yamauchi et al concluded that decreased adiponectin production is implicated in the development of insulin resistance in mouse models of both obesity and lipoatrophy. Their data also indicate that administration of adiponectin might provide a novel treatment modality for insulin resistance in type 2 diabetes.

References

1. Saltiel AR. You are what you secrete. *Nature Med* 7:887-888,2001.
2. Berg AH, et al. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nature Med* 7:947-953,2001.
3. Yamauchi T, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nature Med* 7:941-946,2001.

Editorial Comment: *Adiponectin is a 247 amino acid protein whose expression in adipose tissue is depressed in obese animals. The plasma concentrations are low in these obese animals and also in obese humans, which is a pattern directly opposite to those of leptin, another adipocyte hormone. As discussed by Yamauchi et al, mice ingesting a high fat diet with increased fat accumulation had low tissue levels of adiponectin mRNA and low serum concentrations. Insulin resistance as reflected by hyperglycemia and hyperinsulinemia occurred.*

Figure



A hypothetical model for the secretion and action of adiponectin. The synthesis and secretion of adiponectin is increased by activation of the nuclear receptor PPAR-γ, and reduced by caloric excess, presumably associated with leptin deficiency or resistance. Once released, adiponectin can directly increase fatty-acid transport, oxidation and dissipation in skeletal muscle, reducing the levels of intramyocellular lipids, thus improving insulin signaling. The protein can also increase the sensitivity of the hepatocyte to insulin, either through a direct action, or indirectly by lowering circulating lipids due to its action on muscle. Thus, administration of adiponectin can result in improved insulin sensitivity and glucose tolerance, and can correct hyperglycemia associated with obesity.

From Saltiel AR. You are what you secrete. *Nature Med* 7:887-888,2001.

Administration of rosiglitazone, an inhibitor of peroxisome proliferator-activated receptor-γ which is an essential element for adipogenesis, increased adiponectin tissue mRNA values and also serum levels. Serum glucose was decreased as were serum levels of insulin.

In other mouse models of obesity (e.g. leptin receptor deficiency), administration of adiponectin lowered blood glucose and insulin values. In another mouse model, a lipodystrophic mouse without fat, serum concentrations of adiponectin were undetectable. Hyperglycemia and hyperinsulinemia were present. Administration of adiponectin lowered serum glucose and insulin levels. Both leptin and adiponectin were required in the lipoatrophic mice to restore serum glucose and insulin values to normal.

In the article by Berg et al, serum glucose concentrations were decreased with the administration of recombinant adiponectin to wild type, leptin deficient, and insulin deficient mice. Berg et al also demonstrated that adiponectin depressed hepatic glucose output in vitro which is thus the second physiological effect that might contribute to enhanced insulin sensitivity. In calorically restricted wild type mice, serum adiponectin concentrations were twice those of freely feeding animals suggesting that this adipokine may be important in prolonging the lives of such animals.

Thus, the data in these manuscripts indicate that adiponectin plays a key role in energy metabolism. It enhances insulin sensitivity by lowering serum and tissue triglyceride values, by uncoupling of oxidative phosphorylation in muscle, and by suppressing hepatic glucose output. In addition to the effects on energy metabolism, adiponectin depresses the inflammatory response that accompanies atherogenesis. Indeed, patients with coronary artery disease have lower plasma adiponectin concentrations than do controls. Adiponectin inhibits inflammation in part by suppressing proliferation of myelomonocytic progenitor cells by accelerating apoptosis. The potential utilization of adiponectin as a therapeutic agent for patients with obesity, diabetes mellitus types 1 and 2, hyperlipidemia, and/or atherogenic disorders is clearly enormous. A lead article regarding Adipose Tissue as an Endocrine Gland will appear soon in GGH.

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Genetic Basis of Stature – Genome-Wide Search for Genes that Influence Normal Adult Height

It is well known that short parents have short children and vice versa, and that variation in normal stature has a strong genetic component. However, despite many decades of interest in the genetics of stature, the relevant genes remain elusive. In fact, the genetics of most common traits and diseases in humans is not well understood. The principal explanation is that the geneticist's primary tool for mapping genes is of only limited power for finding genes that have modest effects, such as those that contribute to common diseases and variable traits such as stature. Recent advances in genomics, however, have made it feasible to apply genome-wide linkage analysis to such entities. Indeed, the group led by Eric Lander has used this approach to identify genetic linkage for adult height.[1]

In total, 2,327 individuals from 483 families were studied. Fifty-eight families resided in the Botnia region of Finland, 183 families were from other areas of Finland, 179 families were from southern Sweden and 63 families were from the Saguenay-Lac-St-Jean region of Quebec. They were originally ascertained to investigate other genetic traits. Males were older than 23.5 years and females older than 21.1 years to exclude individuals still growing. The original genotyping results that were based on average spacing of microsatellite markers from 6.5 cM to 12.5 cM depending on the study population, were reanalyzed using the variance-components method implemented in the GENE-HUNTER 2 protocol. The method uses nonparametric multipoint approaches to generate LOD scores for chromosomal locations that reflect the likelihood that genotype data being observed is due to linkage relative to the absence of linkage.

Evidence for linkage was detected in four instances. A LOD score of 3.85 was obtained for linkage at chromosome 6q24-25 in Botnia. A score of 3.40 was calculated for a marker located at 7q31.3-36 in Sweden. A LOD score of 3.35 was determined for markers at 12p11.2-q14 in Finland and a score of 3.56 was found in Finland for 13q32-33. The authors note that a companion study also detected linkage at chromosome 7 site.[2]

The authors are optimistic that they have identified chromosomal regions where genes that influence stature reside, especially on chromosome 7. However, they caution that definitive interpretation is difficult in the absence of confirmation of linkage in additional populations. They observe their results were inconsistent across the four study groups, but note that this is typical in linkage studies of common diseases. They discuss possible reasons for the inconsistency including variation in sampling, existence of genetic variation in different populations and statistical fluctuations and false positives due to unknown causes.