Extending the glucose/fatty acid cycle: a glucose/adipose tissue cycle

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Abstract

It is now recognized that the WAT (white adipose tissue) produces a variety of bioactive peptides, collectively termed ‘adipokines’. Alteration of WAT mass in obesity or lipodystrophy affects the production of most adipose secreted factors. Since both conditions are associated with insulin resistance, the idea has emerged that certain adipokines might influence insulin action. Among these, tumour necrosis factor α, interleukin-6 and resistin are increased in the obese state and interfere negatively with insulin-mediated processes. Conversely, leptin and adiponectin exert an insulin-sensitizing effect, at least in part by favouring tissue fatty-acid oxidation through AMP-activated kinase activation. Obesity-induced insulin resistance has been linked to leptin resistance and decreased plasma adiponectin, while administration of leptin and adiponectin normalizes plasma levels in lipodystrophic mice and reverses insulin resistance. Thiazolidinedione anti-diabetic agents increase endogenous adiponectin production in rodents and humans, suggesting that drugs targeting adipokines might represent a new therapeutic approach to sensitize peripheral tissues to insulin.

Introduction

During the past decade, evidence has been provided that WAT (white adipose tissue) secretes a number of bioactive molecules, collectively termed ‘adipokines’. This newly discovered secretory function has shifted our view of WAT, which is no longer considered only as an energy-storage tissue but also as an endocrine organ influencing whole-body homeostasis. Virtually all known adipokines are dysregulated when WAT mass is substantially altered, as in obesity or lipodystrophic syndromes. Since both conditions are highly associated with insulin resistance, the idea has emerged that WAT might influence glucose homeostasis not only by releasing fatty acids that inhibit insulin action via Randle’s effect in insulin-sensitive tissues, but also through secreted peptides. Indeed, WAT produces several factors that interfere either negatively or positively with insulin-mediated processes in distant tissues. Moreover, TZD (thiazolidinedione) anti-diabetic agents appear to exert their insulin-sensitizing effect at least in part by altering adipose production of certain adipokines, as described below. This article reviews the arguments implicating adipokines as molecular links between WAT and insulin resistance.

TNFα (tumour necrosis factor α), IL (interleukin)-6 and resistin

WAT produces a number of pro-inflammatory cytokines in the absence of inflammation. These include TNFα and several ILs (reviewed in [1,2]). TNFα was the first adipose-secreted product proposed to represent a molecular link between obesity and insulin resistance (reviewed in [3,4]). Indeed, TNFα is overexpressed in WAT in obesity and decreases with weight loss and improvement of insulin sensitivity. A number of studies have demonstrated that TNFα alters insulin signalling in cultured cells and in vivo. Anti-TNFα antibodies ameliorate insulin sensitivity in obese rodents and TNFα-deficient mice are protected from obesity-induced insulin resistance on a high-fat diet. Finally, TZDs repress TNFα gene expression in WAT and prevent TNFα-induced insulin resistance in the rat. However, there is no evidence that WAT is a net exporter of TNFα in humans, suggesting that the cytokine might exert a local paracrine action rather than a systemic function. By contrast, adipose tissue in humans produces significant amounts of IL-6 and this secretion might represent 10–30% of circulating levels [2]. Plasma IL-6 is highly correlated with body mass and inversely related to insulin sensitivity [5–7]. Recent data suggest that IL-6 plays a direct role in insulin resistance by altering insulin signalling in hepatocytes. This effect is mediated by the induction of SOCS-3 (suppressor of cytokine signalling-3), which inhibits insulin-dependent insulin receptor autophosphorylation [8,9].

A newcomer in the dark side of adipose secretion is resistin [10], also known as ADSF for adipose tissue-specific secretory factor [11]. This adipokine, which belongs to a family of cysteine-rich secreted proteins named FIZZ (found in inflammatory zone), has been proposed as a WAT-derived mediator of insulin resistance (reviewed in [12,13]). In the initial report of Steppan et al. [10], immunodetected resistin was found to be increased in plasma of mice with diet-induced and genetic forms of obesity. Later on, however, mRNA levels were reported to be decreased in WAT of obese rodents [14,15]. Recombinant resistin promoted systemic...
insulin resistance in mice and decreased insulin-stimulated glucose transport in adipose cells, while an anti-resistin antibody produced the opposite effect [10]. More recently, infusion of resistin in the rat was shown to induce severe hepatic insulin resistance accounted for by an increased rate of glucose production [16]. Although resistin was originally cloned on the criterion of being reduced by TZDs, treatment of animals with insulin-sensitizing drugs has produced inconsistent patterns of resistin expression. Finally, there is little indication that human resistin influences insulin sensitivity [17]. Identification of the receptor and signalling pathways and analysis of the phenotypes resulting from deletion or overexpression of resistin in transgenic mice will help to further define the biological roles of resistin.

**Leptin**

The discovery of leptin as a crucial factor involved in long-term regulation of food intake and body-weight homeostasis has significantly broadened our understanding of the mechanisms underlying the development of obesity and its complications. The tremendous amounts of information currently available on leptin have been extensively reviewed in the literature and only some important elements will be summarized here. Demonstration of the role of leptin in body-weight homeostasis was provided by a mutation (ob) which occurred spontaneously in mice more than 50 years ago. Since then, ob/ob mice have been bred in animal facilities, allowing the discovery of the leptin [18] and leptin receptor [19] genes. The potent effect of recombinant leptin to reduce food intake, body weight and WAT mass in leptin-deficient mice brought the ultimate proof that the absence of functional leptin is responsible for the obese phenotype of ob/ob mice. The same holds true in humans, where three massively obese children with no functional leptin are currently successfully being treated with leptin [20]. By contrast, rodents and three known individuals carrying a mutation in the leptin receptor gene are resistant to the food-reducing effect of leptin. Common obesity is also characterized by leptin resistance, since circulating leptin levels are increased in proportion to body-fat mass in the general population. However, apart from mutations in the leptin receptor gene, the cellular and molecular mechanisms leading to leptin resistance are still unknown.

Both leptin-deficient and leptin-resistant obese rodents exhibit severe insulin resistance. This condition is rapidly ameliorated by leptin administration in deficient mice, even before reduction of body weight. Moreover, the insulin-sensitizing effect of leptin exceeds that seen in pair-fed animals. Accumulating evidence suggests that leptin promotes fatty acid oxidation and reduces ectopic fat accumulation in non-adipose tissues, thereby increasing insulin sensitivity [21,22]. This effect is mediated by activation of the AMPK (AMP-activated kinase) by leptin, through a direct effect on certain skeletal muscles and indirectly through the hypothalamic–sympathetic nervous system axis [23]. As a result of AMPK activation, the enzyme acetyl-CoA carboxylase is inhibited, leading to reduced intracellular levels of the metabolite malonyl-CoA. This alleviates inhibition of fatty acid entry into the mitochondria by malonyl-CoA and favours fatty acid oxidation. Although of little help in leptin-resistant obese patients, leptin administration has been proposed as a new treatment to ameliorate insulin sensitivity in lipatrophic diabetes, where low leptin levels prevail [24,25].

**Adiponectin**

In the mid-1990s, an adipose-secreted protein that had homology with the complement factor C1q was cloned independently by different groups and named adipQ, Acrp30, apM1, GBP28 and adiponectin (reviewed in [26,27]). Adiponectin is abundantly expressed in adipose cells and its plasma concentration is in the 100-nM range. Structurally, it consists of a collagenous tail and a globular head, which form trimer/dimers and high-molecular-mass complexes in the circulation. Different properties have been ascribed to various recombinant or processed forms (globular head) of the protein and the actual bioactive form(s) has not yet been unequivocally determined [28].

In sharp contrast to most adipokines, adiponectin expression and serum concentrations are not increased but reduced in a variety of obese and insulin-resistant states. In rhesus monkeys, plasma adiponectin decreases along with the development of insulin resistance associated with obesity and aging [29]. Similarly, two case-control studies, in the obesity-prone Pima Indians and in the general population, suggest that individuals with high adiponectin concentrations are less likely to develop type 2 diabetes than those with low concentrations [30,31]. Nutritional and therapeutic manipulations that ameliorate insulin sensitivity, like weight loss, caloric restriction and TZD treatment, all increase adiponectin [32–36]. Conversely, TNFα and IL-6 are potent inhibitors of adiponectin expression and secretion in human WAT biopsies or cultured adipose cells [35,37]. This suggests that TNFα- and IL-6-induced insulin resistance might rely, in part, on an autocrine/paracrine inhibition of adiponectin release.

A series of recent studies, discussed in detail in [26,27], reveal that administration of recombinant adiponectin, either full length or in the form of its isolated globular head, exerts glucose-lowering effects and ameliorates insulin resistance in mice models of obesity or diabetes. In addition, adiponectin has anti-atherogenic properties, as shown by its capacity to suppress macrophage to foam cell transformation in vitro [38]. The phenotype of adiponectin-null mice confirmed the protective role of the protein against atherosclerosis and diet-induced insulin resistance [39–41], although in one study adiponectin-null mice did not show aggravated insulin resistance on a high-fat diet as compared with wild-type mice [42]. Interestingly, insulin resistance in lipatrophic mice is fully reversed by a combination of physiological doses of adiponectin and leptin, but only partially by either adiponectin or leptin alone [43]. This suggests that adiponectin and
leptin may work hand in hand to sensitize peripheral tissues to insulin. However, the two adipokines have both overlapping and distinct functions, since globular adiponectin ameliorates insulin resistance but not obesity in the ob/ob leptin-deficient mice [44].

The insulin-sensitizing effect of adiponectin is mediated, at least in part, by an increase in fatty-acid oxidation through activation of AMPK in skeletal muscles [45,46], similar to the action of leptin. Moreover, adiponectin also activates AMPK in the liver, resulting in reduced rate of hepatic glucose production [45,47] and in isolated rat adipose cells, thereby increasing glucose uptake [48]. Although the signalling pathways evoked by adiponectin are not fully deciphered, two receptors have been recently cloned, Adipo R1 and Adipo R2, that are expressed predominantly in muscle and liver, respectively. These receptors are predicted to contain seven transmembrane domains, but do not seem to be coupled with G-protein [49].

Is that all?
Finally, the list of adipokines influencing insulin sensitivity might not be complete. A clue in favour of this hypothesis was given recently by the outcome of knocking out the insulin-sensitive glucose transporter GLUT 4 selectively in WAT in mice. As expected, these transgenic mice display markedly reduced rates of insulin-stimulated glucose uptake in WAT. Unexpectedly, however, they also develop insulin resistance in muscles, despite preservation of GLUT 4, and in the liver [50]. This suggests that an adipose-secreted factor capable of modulating insulin action in muscles and liver is altered when glucose utilization is reduced in the adipose cells. To our knowledge, this factor has not been determined yet.

Conclusion
Through its secretory function, WAT lies at the heart of a complex network of factors capable of either ameliorating (leptin, adiponectin) or reducing (TNFα, IL-6, resistin) insulin action in relevant tissues, including skeletal muscles and the liver (Figure 1). This raises the possibility that the development of drugs targeting adipose secreted factors or their cognate receptors represents a new therapeutic approach to sensitize peripheral tissues to insulin. This could be of particular therapeutic benefit in pathology associated with WAT mass dysregulation, such as lipodystrophy and obesity.

References