Review

Regulation of adipocytokines and insulin resistance

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Abstract

It has long been known that obesity and insulin resistance are linked. Recently, it has been shown that adipocytes secrete several proteins including tumour necrosis factor- α , interleukin-6, resistin, and adiponectin. Since several of these so-called adipocytokines influence insulin sensitivity and glucose metabolism profoundly, they might provide a molecular link between increased adiposity and impaired insulin sensitivity. Thiazolidinediones which decrease insulin resistance and are used in the treatment of Type 2 diabetes seem to mediate part of their insulin-sensitising effects via modulation of adipocytokine expression.

Furthermore, hormones such as β -adrenergic agonists, insulin, glucocorticoids, and growth hormone might impair insulin sensitivity at least in part via up-regulation or down-regulation of adipocytokine synthesis. We summarise the current knowledge on how major adipocyte-secreted proteins are regulated by hormones and drugs influencing insulin sensitivity and discuss its implications for insulin resistance and obesity. [Diabetologia (2003) 46:1594–1603]

Keywords Adipocytokine, adiponectin, adrenergic, glucocorticoid, growth hormone, insulin, insulin resistance, interleukin-6, leptin, obesity, resistin, tumour necrosis factor α .

Adipocytokines—emerging regulators of insulin sensitivity

Type 2 diabetes is one of the most common chronic diseases, affecting about 150 million people world wide [1]. It is characterised by insulin resistance of peripheral tissues such as liver, muscle, and fat which cannot be overcome by hypersecretion of pancreatic beta cells [2]. Insulin resistance is often associated

with increased body weight and recently, various adipocyte-secreted proteins have been described which are altered in obesity, affect insulin sensitivity and might, therefore, provide a link between these two pathological states (Fig. 1).

This review first summarises drugs and hormones which influence insulin sensitivity and regulate adipocytokine expression. Then, adipocytokines are introduced with emphasis on resistin and adiponectin, and

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Abbreviations: 11 β -HSD1, 11 β -Hydroxysteroid dehydrogenase type 1; ACC, acetyl coenzyme A carboxylase; AMPK, adenosine monophosphate kinase; PI, phosphatidylinositol; PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinedione.

Fig. 1. Adipocytokines which have been implicated in the pathogenesis of insulin resistance and obesity

the current knowledge on how they are regulated in insulin resistance, obesity, and by insulin sensitivity-altering drugs and hormones is summarised. Furthermore, implications for the pathogenesis of insulin resistance and obesity are discussed.

Hormones and drugs influencing insulin sensitivity

Thiazolidinediones (TZDs) are a new class of drugs used in the treatment of diabetes mellitus which profoundly improve insulin sensitivity [3]. On the molecular level, they act as agonists of peroxisome proliferator-activated receptor (PPAR) γ a transcription factor predominantly found in fat [4]. Evidence from clinical and animal studies suggests that increased activity of the sympathetic nervous system contributes to insulin resistance [5]. On the molecular level, β -adrenergic activation inhibits insulin signalling molecules such as IRS proteins which have been shown to be essential for insulin action [6, 7, 8]. Furthermore, β -adrenoceptor stimulation is a strong activator of lipolysis which leads to increased serum concentrations of NEFA and subsequently NEFA can cause insulin resistance at least partly by inhibiting insulin signalling [9]. In fact, it has been suggested that apart from β -adrenergic agonists various adipocytokines including TNF- α and IL-6 also induce insulin resistance by stimulating lipolysis in fat cells in an autocrine manner thereby increasing systemic NEFA concentrations [10]. Interestingly, serum concentrations of NEFA are already increased before the onset of Type 2 diabetes [11]. Hyperinsulinaemia associated with peripheral insulin resistance is an integral part in the development of Type 2 diabetes and down-regulation of insulin signalling molecules probably contributes to impairment of insulin sensitivity found in states of increased insulin serum concentrations [1, 12]. Glucocorticoids cause insulin resistance in vivo; however, it is not

clear, to what extent increased glucocorticoid concentrations contribute to insulin resistance seen in obesity [13]. Furthermore, growth hormone potently antagonises insulin action in insulin-sensitive tissues such as muscle, fat, and liver in vivo and in vitro [14, 15]. Thus, insulin resistance in rats caused by chronic growth-hormone treatment is accompanied by a decrease in insulin-stimulated insulin receptor activity and IRS protein phosphorylation in vivo [16, 17].

TNF- α

TNF- α has early been implicated as an important regulator of insulin sensitivity at least in rodents [18]. Thus, TNF- α induces serine phosphorylation of IRS-1 in vitro and serine-phosphorylated IRS-1 acts as an inhibitor of insulin receptor kinase activity and downstream signalling including phosphatidylinositol (PI) 3-kinase activation [19]. Furthermore, TNF- α induces lipolysis and down-regulates IRS-1 and the insulin-sensitive glucose transporter (GLUT)-4 [20]. Moreover, it has been shown that membrane-associated TNF- α , which is up-regulated in obesity, can act in an autocrine manner thereby altering adipose biology profoundly [21, 22]. Neutralisation of TNF- α improves insulin sensitivity in *fa/fa* rats but not in obese diabetic humans [18, 23, 24].

Various animal models of genetically determined insulin resistance and obesity, including *ob/ob*, *db/db* mice, as well as *fa/fa* rats, overexpress TNF- α (Table 1) [25]. In humans, TNF- α mRNA and protein expression in fat are low but positively correlate with body adiposity, and decrease in obese subjects after weight loss [26, 27]. However, TNF- α serum concentrations are indistinguishable between insulin-resistant and insulin-sensitive subjects matched for BMI [11].

Troglitazone suppresses TNF- α mRNA expression in fat of obese Zucker rats in vivo suggesting that this

Table 1. Regulation of adipocytokines by obesity, TZDs, and insulin resistance-inducing hormones

Adipocytokine	Obesity	TZDs	β -agonists	Insulin	Glucocorticoid	GH	TNF α
TNF- α	$\uparrow$ [25, 26, 27]	($\downarrow$) [28, 29]	$\uparrow$ [30]	$\leftrightarrow$ [29]	($\downarrow$) [29, 32]	$\downarrow$ [33, 34, 35]	
IL-6	$\uparrow$ [42, 43, 44]	$\leftrightarrow$ [45]	$\uparrow$ [46, 47, 48, 49]	$\uparrow$ [46, 49]	$\downarrow$ [46, 48, 49, 50, 51]	$\uparrow\downarrow$ [46, 53]	$\uparrow$ [46, 54]
Resistin	$\uparrow\downarrow$ [55, 56, 58, 59, 60, 61, 62, 63, 64]	$\uparrow\downarrow$ [55, 60, 64, 65, 66, 67]	($\downarrow$) [65, 66, 68]	$\uparrow\downarrow$ [60, 65, 66, 69, 70]	($\uparrow$) [65, 66, 68]	($\uparrow\downarrow$) [65, 71, 72]	$\downarrow$ [65, 71]
Adiponectin	$\downarrow$ [75, 88, 89]	$\uparrow$ [78, 92, 93, 94, 95, 96]	$\downarrow$ [97, 98, 99, 100]	$\uparrow\downarrow$ [93, 102, 103, 104, 105]	$\downarrow$ [99, 102, 105, 106, 107]	$\leftrightarrow$ [102]	$\downarrow$ [92, 100, 102]
Leptin	$\uparrow$ [109, 110, 111]	$\downarrow$ [113, 114, 115, 116]	$\downarrow$ [117, 118]	$\uparrow$ [49, 119, 120, 121]	$\uparrow$ [49, 118, 122]	$\downarrow$ [124, 125, 126, 127, 128]	

$\uparrow$ indicates up-regulation, $\downarrow$ down-regulation, $\leftrightarrow$ no regulation. $\uparrow\downarrow$ indicates that contradictory results have been published showing both, up-regulation and down-regulation by the same

hormone, () indicates that not all studies have demonstrated this regulation. References which are explained in greater detail in the text are given

adipocytokine might be one target of the insulin-sensitising effects of this drug (Table 1) [28]. However, another study could not find any influence of rosiglitazone on TNF- α release of human adipocytes in vitro indicating that the in vivo effects of TZDs are indirect [29]. β -adrenergic stimulation by isoproterenol increases TNF- α secretion almost twofold in vivo (Table 1) [30]. This positive effect might be mediated by activation of lipolysis since NEFA are strong physiological inducers of TNF- α expression in fat and mice lacking the adipocyte fatty-acid binding protein aP2 do not express this adipocytokine in white adipose tissue [31]. In one study an influence of insulin and the glucocorticoid cortisol on TNF- α secretion has not been found in human adipocytes in vitro (Table 1) [29]. In contrast, chronic treatment with dexamethasone for 15 days inhibits TNF- α mRNA expression in human immortalised PAZ6 preadipocytes (Table 1) [32]. Furthermore, two independent studies report decreased TNF- α mRNA and serum concentrations after transgenic growth hormone overexpression suggesting that growth hormone is a negative regulator of this adipose-expressed protein (Table 1) [33, 34]. In accordance with this view, TNF- α concentrations are increased in serum and per kg fat mass in growth hormone-deficient patients as compared to the control subjects matched for age [35].

Taken together, these studies suggest that TNF- α is increased in adipocytes in obesity and that TZDs and β -adrenoceptor stimulation might modulate insulin sensitivity at least partly by regulating this adipocytokine.

Interleukin-6

IL-6 has originally been cloned as a leucocyte-derived proinflammatory protein. Since about 30% of systemic IL-6 is secreted by adipose tissue, this protein is also an adipocytokine [36]. IL-6 influences insulin sensitivity via distinct mechanisms. Thus, IL-6 derived from omental fat depots flows directly into the liver and might, thereby, stimulate hepatic triglyceride secretion [37]. Furthermore, IL-6 directly impairs insulin signalling in primary mouse hepatocytes and 3T3-L1 adipocytes with decreased activation of IRS-1 and PI 3-kinase, as well as impaired insulin-induced glycogenesis in liver cells [38, 39]. Administration of recombinant IL-6 in rodent models and humans in vivo induces hepatic gluconeogenesis which, in turn, leads to hyperglycaemia and compensatory hyperinsulinaemia [40, 41].

IL-6 plasma concentrations are statistically significantly up-regulated in murine and human insulin resistance and obesity [42] and IL-6 concentrations at baseline independently predict future risk of developing Type 2 diabetes mellitus (Table 1) [43, 44].

There have not been any studies so far indicating that TZDs used in clinical practice directly influences

Fig. 2. IL-6 is up-regulated by various hormones inducing insulin resistance whereas adiponectin expression is suppressed. Furthermore, recent data suggest that IL-6 induces its own expression via a positive feedback loop and adiponectin mRNA expression and protein secretion are down-regulated by this proinflammatory adipocytokine. Since adiponectin has been suggested to be an insulin-sensitising adipocytokine whereas IL-6 induces insulin resistance, this regulation might have important implications in the pathogenesis of diabetes mellitus and obesity

IL-6 gene expression in adipocytes. Thus, 26 weeks of rosiglitazone treatment does not affect IL-6 serum concentrations in one study (Table 1) [45]. β -adrenergic activation stimulates IL-6 mRNA expression in 3T3-L1 adipocytes and this effect is mediated via a classic G_s-protein-coupled pathway (Table 1) [46]. In accordance with these findings, IL-6 protein secretion was increased in human adipocytes in vitro and in vivo in volunteers after treatment with the β -adrenoceptor agonist isoprenaline [47, 48, 49]. Furthermore, insulin stimulates and glucocorticoids suppress IL-6 mRNA and protein expression in 3T3-L1 and human adipocytes (Table 1) [46, 48, 49, 50]. In accordance with these in vitro results, diminished exercise-induced IL-6 plasma concentrations have been found after treatment with hydrocortisone or dexamethasone in vivo [51]. These results are consistent with the anti-inflammatory effect of glucocorticoids used in clinical medicine and indicate that IL-6 is not a candidate to mediate glucocorticoid-induced insulin resistance [52]. Growth hormone also profoundly affects IL-6 gene expression in vitro since a maximal sixfold stimulation of IL-6 mRNA could be observed 1 h after adding growth hormone to 3T3-L1 adipocytes with sustained up-regulation persisting for at least 24 h (Table 1) [46]. However, recombinant growth hormone treatment of growth hormone-deficient men for 18 months significantly decreases IL-6 plasma concentrations [53]. Thus, the in vitro results obtained in mouse 3T3-L1 adipocytes might not reflect in vivo conditions found in growth hormone-deficient patients. TNF- α potently induces IL-6 mRNA expression and secretion in differentiated 3T3-L1 adipocytes (Ta-

ble 1) [46, 54]. Interestingly, our group has recently shown that IL-6 stimulates its own sustained expression in 3T3-L1 adipocytes (Fig. 2) [46].

Taken together, results of the studies summarised above suggest that β -agonists, insulin, TNF- α , and possibly growth hormone might mediate their insulin resistance-inducing effects at least in part via up-regulation of IL-6 expression in adipocytes. Furthermore, preliminary in vitro evidence from our group indicates that a positive feedback loop exists in adipocytes promoting sustained IL-6 up-regulation even when the primary insulin resistance-inducing hormone is no longer active.

Resistin

Recently, the new adipocytokine resistin has been isolated [55, 56]. It was suggested that this adipocyte-secreted protein impairs glucose tolerance [55]. In accordance with this view, resistin induces severe hepatic but not peripheral insulin resistance [57]. Furthermore, it was initially shown that resistin is up-regulated in both genetic and diet-induced obesity in vivo and down-regulated by TZDs [55]. On the basis of these observations, it has been postulated that resistin might be both a link between obesity and diabetes, as well as a candidate to explain the anti-diabetic effects of TZDs [55]. However, several studies indicate that resistin's role in insulin sensitivity and TZD action—if it has one at all—is much more complex. First, it is not clear whether human adipocytes express substantial amounts of resistin mRNA and protein [58, 59]. Secondly, results from studies determining expression and regulation of this adipocytokine are contradictory. Thus, severely decreased resistin mRNA levels have been observed in different mouse models of obesity and insulin resistance such as *ob/ob*, *db/db*, *tub/tub*, and *KKAY* mice (Table 1) [60]. These findings are supported and extended by other groups indicating that resistin is down-regulated in diet-induced obesity in mice [61], in fructose-fed obese rats [62], in *fa/fa* rats [63], and in KK mice [64]. Paradoxically, weight loss further inhibits resistin mRNA expression in obese *fa/fa* rats [63]. Furthermore, it is not clear whether PPAR γ -agonists consistently suppress resistin gene expression (Table 1). In accordance with the original observations, PPAR γ -activators such as troglitazone, rosiglitazone, and darglitazone potently down-regulate resistin mRNA by approximately 80% to 90% in 3T3-L1 adipocytes in vitro [65, 66] and resistin mRNA is down-regulated by 72% in *db/db* mice after rosiglitazone treatment [67]. In contrast, up-regulation of resistin mRNA expression has been observed after treatment of male *ob/ob* mice and ZDF rats with the PPAR γ -agonists MC-555, rosiglitazone, and GW1929 for 7 days [60]. Similarly, consistent up-regulation of resistin mRNA has been shown in white fat after treatment with the PPAR γ -agonists NC-2100,

pioglitazone, and troglitazone [64]. Various hormones regulate resistin mRNA and protein expression in vivo and in vitro; however, again results are often contradictory. Thus, one report from our group shows that β -adrenergic activation potently down-regulates resistin mRNA expression by up to 80% in 3T3-L1 adipocytes (Table 1) [68]. Furthermore, this effect is probably Gs-protein-coupled since cholera toxin, forskolin, and dibutyryl-cAMP which all activate key signalling molecules of this pathway decrease resistin gene expression [68]. Because β -adrenergic activation is a potent activator of lipolysis in fat cells and NEFA inhibit resistin gene expression in rat adipocytes, β -adrenoceptor stimulation might mediate its inhibitory effect via increased NEFA concentrations [62]. Down-regulation of resistin mRNA and protein by β -adrenergic activation has been confirmed in one study [65], whereas recently, down-regulation of this adipocytokine only by forskolin but not by isoproterenol has been reported [66]. Furthermore, insulin down-regulates resistin gene expression in 3T3-L1 adipocytes in vitro (Table 1) [65, 66]. However, administration of insulin to streptozotocin-diabetic mice [69] or ZDF rats [60] consistently stimulates resistin mRNA synthesis in vivo and a dose-dependent increase of 3T3-L1 adipocyte resistin secretion after insulin treatment for 24 h has been described [70]. Two independent studies suggest that the glucocorticoid dexamethasone induces resistin mRNA and protein expression in 3T3-L1 fat cells by up to 3.5-fold [65, 66]; however, a third study from our laboratory did not find any effect in the same cell line (Table 1) [68]. Growth hormone suppresses resistin mRNA and protein expression between 30% and 50% in 3T3-L1 adipocytes (Table 1) [65]. In contrast, in studies from our laboratory resistin mRNA expression is not affected by growth hormone [71]. Furthermore, 24-h infusion of growth hormone into spontaneous dwarf rats which lack growth hormone increases resistin expression in white adipose tissue by almost tenfold in vivo [72]. Moreover, two independent studies show that TNF- α is a potent negative regulator of resistin mRNA expression and secretion with up to 90% inhibition detectable after TNF- α treatment (Table 1) [65, 71].

Taken together, it has been clearly shown during the last two years that resistin mRNA expression is regulated by various hormones and drugs influencing insulin sensitivity. However, often fundamentally contradictory results have been published and it is safe to conclude that resistin's role in the regulation of glucose homeostasis is probably not as prominent as implicated by the original study.

Adiponectin

Adiponectin has originally been cloned by four independent groups using different experimental ap-

proaches [73, 74, 75, 76]. Since 2001 it has become apparent that adiponectin influences insulin sensitivity profoundly. Thus, a globular C-terminal fragment of adiponectin is able to reduce plasma glucose concentrations and an increase in fatty acid oxidation in muscle might contribute to this effect [77]. These observations are confirmed and extended by two other studies [78, 79]. The authors show that a globular fragment as compared to full length adiponectin increases fatty acid combustion in muscle cells much more potently, thereby reducing plasma glucose concentrations [78]. Furthermore, activation of adenosine monophosphate kinase (AMPK) followed by inhibition of acetyl coenzyme A carboxylase (ACC) by adiponectin might be a mechanism by which this effect is mediated [79, 80]. In contrast, two studies suggest that only full-length, but not globular adiponectin, potently augments insulin-induced inhibition of glucose output in liver cells in vivo and in vitro [79, 81]. Again, stimulation of AMPK leading to decreased concentrations of gluconeogenic enzymes in liver might be a mechanism for this effect [79]. Further support for adiponectin being an endogenous insulin sensitizer comes from knock-out studies. Two independent studies show impaired insulin sensitivity in adiponectin knockout mice whereas one study does not [82, 83, 84]. Adiponectin seems to protect mice from atherosclerosis [83, 85]. Furthermore, data indicate that low adiponectin serum concentrations at baseline independently predict the future risk of developing Type 2 diabetes mellitus in humans [86]. Most recently, two different adiponectin receptors have been cloned which need to be characterised further [87].

Adiponectin mRNA expression in fat and plasma concentrations are decreased in insulin resistance and obesity (Table 1) [75, 88, 89]. In accordance with these findings, adiponectin expression increases with improved insulin sensitivity and weight loss [63, 90, 91]. As an exception, exercise does not appear to influence adiponectin expression despite its profound insulin-sensitising effect [91]. Adiponectin mRNA synthesis and secretion are increased by TZDs in vitro and in vivo (Table 1) [78, 92, 93, 94, 95]. Thus, treatment of diabetic patients with rosiglitazone for 6 months increases adiponectin plasma concentrations twofold without significant changes in the placebo group [95]. Even treatment of normal insulin-sensitive subjects with rosiglitazone for 2 weeks results in a 130% increase in adiponectin plasma concentrations [96]. Various hormones inducing insulin resistance down-regulate adiponectin expression. Thus, β -adrenergic activation inhibits adiponectin mRNA expression by up to 75% in differentiated 3T3-L1 cells in vitro (Table 1) [97]. Similarly, adiponectin mRNA and protein synthesis are down-regulated in human adipocytes in vitro by β -adrenoceptor agonists with β_3 -agonists having the most potent effects [98]. Independent studies suggest that the effect of β -adrenergic stimula-

tion on adiponectin gene expression is mediated by G_s -protein coupled pathways [97, 99, 100]. β -adrenergic stimulation and cAMP might decrease adiponectin expression via increased lipolysis and NEFA. However, short-term infusion of NEFA for up to 7 h does not alter adiponectin serum concentrations in humans in vivo [101]. The influence of insulin on adiponectin gene expression and protein synthesis is less clear. A study from our laboratory shows that chronic treatment with insulin reduces adiponectin mRNA expression in 3T3-L1 adipocytes in vitro (Table 1) [102]. These findings are in accordance with in vivo studies indicating that fasting insulin concentrations are negatively correlated with adiponectin plasma concentrations [93, 103]. In contrast, in human white and mouse brown adipocytes, adiponectin mRNA synthesis is in fact stimulated by insulin [104, 105]. Glucocorticoids decrease adiponectin mRNA expression in 3T3-L1 cells, as well as human adipocytes (Table 1) [102, 105]. These changes on the mRNA level are paralleled in vitro by a decrease in adiponectin protein secretion [99]. In accordance with these in vitro findings, removal of the adrenal gland in *ob/ob* mice leading to decreased concentrations of glucocorticoids increases adiponectin mRNA in fat and plasma concentrations in vivo [106]. In addition, transgenic over-expression of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) in fat tissue, which significantly increases local glucocorticoid concentrations, decreases adiponectin mRNA expression in vivo [107]. Interestingly, a sexual dimorphism exists with plasma adiponectin concentrations being significantly lower in men as compared to women [108]. In accordance with this observation testosterone inhibits adiponectin secretion in 3T3-L1 adipocytes [108]. Furthermore, various studies indicate that adiponectin mRNA expression and protein secretion are decreased in mouse 3T3-L1 adipocytes and human primary adipocytes after TNF- α treatment (Table 1) [92, 100, 102]. Recent work from our group shows down-regulation of adiponectin secretion to 75% and mRNA expression to 50% of control levels by IL-6 in 3T3-L1 adipocytes in vitro (Fig. 2) [99].

Taken together, studies on the regulation of adiponectin indicate that this adipocytokine is up-regulated by insulin-sensitising TZDs and suppressed by β -adrenoceptor agonists, glucocorticoids, TNF- α , and IL-6, supporting the role of adiponectin as an important endogenous insulin sensitizer.

Leptin

Leptin was originally cloned in 1994 as the protein product of the *ob* gene mutation which leads to massive obesity in *ob/ob* mice [109]. Leptin inhibits appetite and weight gain by decreasing orexigenic and increasing anorexigenic peptide expression in the hypo-

thalamus [109]. Studies concerning direct effects of leptin on insulin sensitivity in insulin-responsive tissues such as liver, muscle, and fat have yielded contradictory results; however, there is general agreement that leptin expression and secretion are increased in obesity and that a strong correlation exists between body fat stores and leptin plasma concentrations (Table 1) [109, 110, 111]. Consistent with its appetite-suppressive effect, leptin expression is stimulated upon feeding and suppressed during starvation [112]. TZDs consistently suppress leptin expression in rodent fat in vivo and in vitro (Table 1) [113, 114, 115, 116]. Furthermore, β -adrenergic activation rapidly decreases leptin expression and secretion in primary adipocytes in vitro and mice in vivo (Table 1) [117, 118]. Insulin is a potent activator of leptin mRNA expression and protein secretion [49] and it is plausible that insulin is the major mediator of increased post-prandial leptin concentrations (Table 1) [119, 120, 121]. Furthermore, glucocorticoids stimulate leptin expression and secretion in vivo and in vitro (Table 1) [49, 118, 122]. Of interest, this increase in leptin synthesis can be reversed by TZD treatment in humans [123]. Furthermore, potent down-regulation of leptin secretion by growth hormone in 3T3-L1 adipocytes overexpressing the human growth hormone receptor has been shown (Table 1) [124]. In a clinical context, leptin concentrations are increased in subjects with growth-hormone deficiency [125, 126] and are lower in acromegaly [127, 128].

Conclusions and perspectives

During the last couple of years it has been shown that adipocytes actively influence insulin sensitivity by secreting NEFA and various adipocytokines. This review summarised recent findings on the regulation of several fat-secreted proteins.

Various important questions have yet to be answered. Whereas regulation of adiponectin and resistin has been determined in detail within the last 2 years, it is still not clear whether these fat-secreted factors might affect the expression of other adipocytokines, thereby influencing insulin sensitivity. Furthermore, striking discrepancies remain between different studies which are sometimes unclear and make safe conclusions difficult to draw. This is especially true for resistin where contradictory results have been published despite similar experimental approaches.

Apart from these uncertainties, it seems safe to conclude that concerning direct modulation of insulin sensitivity, adiponectin and IL-6 are the most interesting adipocytokines for the following reasons: firstly, both adipocyte-secreted proteins are expressed in substantial amounts in both mice and humans. In contrast, consistent and significant expression and secretion of TNF- α and resistin has only been shown in fat of ro-

dents but not of humans. Secondly, several independent studies show up-regulation of IL-6 and suppression of adiponectin in insulin resistance and obesity in mice and humans. Prospective studies indicate that patients are at a high risk of developing diabetes mellitus if IL-6 concentrations are high and adiponectin is low. For resistin, the studies are inconsistent and mostly restricted to rodents. TNF- α concentrations are clearly increased in human obesity but are not significantly different between insulin-sensitive and insulin-resistant probands when body weight is matched. Thirdly, recent studies suggest that IL-6 decreases and adiponectin increases insulin sensitivity when administered in vivo although the signalling pathways are not completely clear. In contrast, almost no data are available concerning mechanisms by which resistin might influence insulin sensitivity. Leptin is undoubtedly a major regulator of appetite and food intake and by altering body mass influences insulin sensitivity profoundly. However, its potential, direct peripheral effects on insulin sensitivity are inconsistent and far from being clear.

Taken together, recent studies suggest that adipocytokines are major regulators of insulin sensitivity potentially linking insulin resistance and obesity. Further work is needed to clearly determine how these adipocytokines are regulated and how they influence insulin signalling in liver, muscle, and fat in rodents and in humans.

Sources. This review is based on the relevant literature published in the English language during the period 1990–2003, and seminal prior contributions. The sources available to the authors were integrated with sources identified through PubMed searches for “regulation, insulin resistance, body weight, obesity, and adipocyte” combined with searches for “adipocytokine, TNF α , IL-6, resistin, adiponectin, and leptin”.

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