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ADIPOKINE EXPRESSION AND SECRETION: A TARGET FOR PHARMACOLOGIC TREATMENT

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Obesity and insulin resistance are important risk factors for major diseases such as metabolic syndrome, type 2 diabetes mellitus, and atherosclerotic cardiovascular disease. Chronic subclinical inflammation appears to underlie these disorders. Increasing evidence suggests that dysregulation of metabolically active adipose tissue contributes to systemic inflammation in part by secreting higher concentrations of pro-inflammatory adipokines (a diverse set of bioactive proteins produced by adipose tissue). Some adipokines act as endocrine factors directly enhancing systemic inflammation. Increased secretion of these adipokines results from local adipose tissue inflammation that is mediated ~~in part~~ by autocrine and~~/or~~ paracrine pathway. Adipokine expression and thus secretion are modulated by intercellular cross talk within adipose tissue, including that between adipocytes and macrophages (and possibly mast cells), as well as by oxidative stress and activation of pro-inflammatory pathways such as nuclear factor kappa B and mitogen-activated protein kinase pathways. These regulators of adipokine expression and secretion may serve as therapeutic targets for pharmacologic agents that ameliorate the above adipokine-related diseases. These agents include the widely used angiotensin II type 1 receptor blockers, inhibitors of angiotensin-converting enzyme, metformin, thiazolidinediones, statins, salicylates, as well as others yet to be developed. ***Biomed Rev 2006; 17: 63-72.***

Key words*:* adipokines*,* adipose tissue, cardiovascular disease, diabetes, drugs

INTRODUCTION

Obesity and insulin resistance are key features of the metabolic syndrome (1) that increases the risk for development of diseases such as atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (2). The rapidly increasing prevalence of these disorders in the last decades poses a challenging healthcare burden in terms of the associated morbidity, mortality, and economic impact. Prevention and treatment of these disorders requires targeting their underlying mechanisms.

Chronic subclinical inflammation appears to underlie obesity and insulin resistance as well as predict the development of T2DM and/or CVD. This systemic inflammation is characterized by elevated concentrations of various circulating pro-inflammatory proteins that act in an endocrine fashion. For example, increased plasma interleukin-6 (IL-6) concentration

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is associated with increased obesity (3), insulin resistance (4), severity of T2DM (5), and cardiovascular complications (6). Plasma concentration of a related pro-inflammatory chemokine, interleukin-8 (IL-8/CXCL8), increases with insulin resistance in abdominally obese male subjects (4) and with atherosclerotic plaque instability in coronary heart disease patients (7). Circulating concentrations of another pro-inflammatory protein, plasminogen activator inhibitor-1 (PAI-1), are also associated with insulin resistance (8), T2DM (9), and an increased risk for developing CVD (10). In addition, elevated concentrations of C-reactive protein (CRP), an acute phase protein, are similarly associated with poor glycemic control in T2DM (11), predict T2DM (8), and constitute a risk factor for ischemic stroke (12). C-reactive protein and serum amyloid A (SAA), another acute phase protein, predict CVD independently of each other (13), even though their serum concentrations are correlated (14). Concentrations of SAA also correlate with obesity (15) and fasting insulin levels, indicating a link to insulin resistance (14).

In addition to the above endocrine factors, systemic concentrations of pro-inflammatory proteins that have generally been considered to act in a paracrine fashion, such as the pleiotropic cytokine tumor necrosis factor-α (TNF-α) (16) and chemokine monocyte chemotactic protein-1 (MCP-1/CCL2) (17, 18), are also associated with both obesity and impaired insulin sensitivity. Furthermore, serum concentrations of TNF-α correlate with those of CRP (19), predict CVD events (20), and are increased in subjects with T2DM (21). Similarly, plasma MCP-1 concentrations are elevated in patients with acute myocardial infarction (22) or acute coronary syndromes (23) compared to those with stable angina, while its concentrations in the latter subjects are higher still than those in people with angiographically normal coronary arteries (24).

In contrast to the above pro-inflammatory proteins, plasma concentrations of adiponectin, an anti-inflammatory protein, inversely correlate with measures of obesity and insulin resistance in non-diabetic subjects (25). Low concentrations of adiponectin predict the progression of T2DM, with the high molecular weight form of adiponectin being a stronger predictor compared to total adiponectin (26). In addition, higher plasma adiponectin concentrations are associated with a lower risk of myocardial infarction independent of glycemic status (27). Taken together, the concerted actions of the above circulating pro- and anti-inflammatory proteins, along with others yet to be discovered, appear critical in linking obesity and insulin resistance with T2DM and CVD.

Adipose tissue may contribute to systemic inflammation as described above by its secretion of pro- and anti-inflammatory proteins, including cytokines, chemokines, acute phase reagents, and growth factors (25-30). These proteins are called adipokines to indicate that they are derived from adipose tissue. It is worth noting that despite this terminology, adipose tissue is not the sole source of most of these bioactive molecules, but such non-adipose sources are not of the present article~~'s scope~~. In this review we thus focus on the adipopharmacology of adipokines as related to obesity and associated diseases.

ADIPOKINES CONTRIBUTE TO SYSTEMIC INFLAMMATION AND RELATED DISEASES

Adipose tissue secretion of various endocrine adipokines contributes significantly to their circulating concentrations, and the tissue expression and/or secretion of these adipokines also correlate with parameters of obesity and insulin resistance. For example, the tissue secretion of adipokine IL-6 may constitute up to a third of its plasma concentration in the absence of any acute inflammation (29). The protein levels of IL-6 in abdominal subcutaneous adipose tissue are higher in obese compared to non-obese subjects (30), and its mRNA levels correlate positively with plasma insulin concentrations in non-diabetic subjects (31). The percentage of body fat as a measure of adiposity appears to account for the negative correlation between plasma IL-6 concentrations and measures of insulin sensitivity in non-diabetic subjects (3). Adipose tissue also appears to be an important source of plasma IL-8. IL-8 secretion by adipose tissue correlates with body mass index (BMI) (32), and thus may contribute significantly to the elevated plasma IL-8 concentration in obese (33) and insulin resistant people (4). Human adipose tissue, particularly adipocytes, selectively and highly expresses SAA (15); this may explain the correlation between its tissue mRNA and protein levels and serum concentrations (14). Similarly, adipose tissue mRNA transcript levels of adiponectin, an abundant adipokine produced predominantly by the tissue (34), correlate with its circulating concentrations (35). Adipose tissue mRNA and protein levels of MCP-1 correlate with its plasma concentrations in animal models of obesity (36,37). Adipose-specific overexpression of MCP-1 in transgenic mice increases its plasma concentrations and results in systemic insulin resistance (38). However, the relationship between MCP-1 expression levels in adipose tissue and its circulating concentrations in

human has not been fully elucidated.

The expression and secretion of the above pro-inflammatory endocrine adipokines may be enhanced by intercellular cross-talk in adipose tissue, such as the interaction between adipocytes and macrophages as an emerging important constituent of the tissue stromovascular fraction. Recent studies demonstrate that the percentage of macrophages in adipose tissue correlates with obesity (39) and insulin resistance (40). The resident macrophages are derived from peripheral blood monocytes that infiltrate into adipose tissue (39). The infiltration process begins with monocyte chemotaxis and adhesion to adipose tissue (41). Once inside the adipose tissue, the monocytes can differentiate into macrophages that have, among many other properties, enhanced inflammatory activity (42), creating a pro-inflammatory loop within adipose tissue through their secretion of TNF-α and IL-1β (43). Both cytokines further induce the transcription of other pro-inflammatory factors, e.g. IL-6 and PAI-1(44). Tumor necrosis factor-α also increases adipose tissue expression levels of IL-8 mRNA (45), while decreasing those of adiponectin (46,47). In addition, TNF-α stimulates free fatty acid release and insulin resistance in adipose tissue (48). These functions of ~~adipokine~~ TNF-α may help explain the associations between the expression levels of TNF-α in adipose tissue with measures of obesity (49) and plasma insulin concentrations (31). A variety of other factors secreted by macrophages and potentially other cell types, such as mast cells (50), in adipose tissue may also modulate adipokine expression and secretion.

MOLECULAR REGULATION OF ADIPOKINE EXPRESSION AND SECRETION

The expression and secretion of the above pro-inflammatory adipokines may be modulated by various molecular factors, such as oxidative stress. Enhanced oxidative stress in adipose tissue is associated with accumulation of adipose tissue mass in obesity (51). The oxidative stress in adipose tissue is manifested in increased reactive oxygen species (ROS) production, elevated expression levels of nicotinamide adenine dinucleotide phosphohydrogenase (NADPH) oxidase and decreased expression levels of anti-oxidative enzymes. Increased oxidative stress in adipocytes as measured by ROS production may be mediated by different pathways, such as protein kinase C-δ (52) and hyperpolarization of the mitochondrial membrane (53). Oxidative stress contributes to adipose tissue inflammation as demonstrated by increased expression levels of IL-6, PAI-1, and MCP-1, and decreased levels of adiponectin ~~(51)~~ in adipocytes exposed to ROS generators such as ~~H2O2~~ or xanthine oxidase. Increased expression and secretion of IL-6 (53) and PAI-1 (54) by adipocytes due to ROS has also been demonstrated using other generators of ROS, such as hyperglycemia (53) and lipid peroxidation (54). Similarly, *in vivo* infusion of angiotensin II induces oxidative stress in adipose tissue as assessed by increased mRNA expression levels of NADPH oxidase components, resulting in decreased adiponectin expression and secretion from adipose tissue (55).

Oxidative stress in adipose tissue stimulates major molecular pro-inflammatory pathways, such as the ubiquitous transcription factor nuclear factor kappa B (NF-κB) pathway (56). Modulated by inhibitor-κ B kinases (IKKα and IKKβ), NF-κB acts as a central regulator of pro-inflammatory response ~~that~~ directly induce~~s~~ adipose tissue transcription of multiple genes encoding pro-inflammatory adipokines, including IL-6 and IL-8 (57) (an extensive list of genes regulated by NF-κB has been compiled at http://bioinfo.lifl.fr/NF-KB/). This regulation may be due in part to the fact that the basal activity of NF-κB increases during adipocyte differentiation from precursor cells (58). Elevated adipose tissue expression of paracrine adipokines regulated by NF-κB, such as MCP-1 (38) and intercellular adhesion molecule 1 (ICAM-1) (59), may facilitate macrophage infiltration of the tissue. Furthermore, resident macrophages may utilize the IKK/NF-κB pathway to augment the self-propagated cycle of inflammation in the tissue, as this pathway appears to mediate the pro-inflammatory effects of macrophage cytokines TNF-α and IL-1β on adipose tissue (57).

In inducing the transcriptional activation of pro-inflammatory genes, NF-κB requires assistance from other transcription factors, such as activating protein 1 (AP-1) (60). The activity of AP-1 transcription factors often depends on the activity of mitogen-activated protein kinase (MAPK) signaling pathway. The MAPK pathway consists of serine/threonine kinases; notably, the mRNA expression levels of several kinases involved in this pathway are increased in adipose tissue from obese compared to lean subjects (61). There are three major groups of classical MAPKs: extracellular signal-regulated kinases (ERK) 1 and 2; c-Jun amino-terminal kinases (JNK) 1, 2, and 3; and p38 MAPK (p38) α, β, γ, and δ (62). The MAPK pathway may specifically contribute to the transcriptional regulation of pro-inflammatory proteins in adipose tissue, because inhibitors of this pathway decrease the tissue secretion of IL-6 (57), IL-8

(57), MCP-1 (63), and TNF-α (64). Furthermore, inhibition of both p38 MAPK and NF-κB pathways in adipose tissue reduces the secretion of MCP-1 to a greater extent compared to inhibition of NF-κB alone (63). In addition, activation of JNK, such as induced by obesity-related endoplasmic reticulum stress (65), may lead to insulin resistance and T2DM (65-67). Taken together, all of the above transcriptional pathways may serve as adipopharmacologic targets for current and new drugs to treat obesity-related diseases.

PHARMACOLOGIC AGENTS MODULATING ADIPOKINE EXPRESSION AND SECRETION

Given the important contribution of adipokines to various diseases as described above, regulation of their expression and secretion serves a therapeutic target. In fact, current approaches to prevent or treat the diseases may achieve their effects in part by reducing the expression and secretion of pro-inflammatory adipokines while stimulating those of anti-inflammatory adipokines. These approaches include lifestyle changes and pharmacologic intervention. The first approach aims to modify behavior by means of diet and exercise, but such efforts typically result in modest outcomes (68). This is presumably due to short duration and/or minimal intensity of the treatments resulting in difficulties to achieve long-term optimal weight maintenance. While the effects of these behavior modifications on adipokine expression and secretion are reviewed elsewhere (69; also see Kroff and E… in this volume of Biomedical Reviews), this review focuses on the second approach using pharmacologic agents. This latter approach is needed especially for those individuals who are unable or unwilling to change their lifestyle.

Anti-oxidants. Despite the accumulating evidence for the role of oxidative stress in regulating adipokine expression and secretion as described above, data are scarce on medications targeting this specific pathway. Nevertheless, the anti-oxidant property of several types of medications may contribute to their effects in improving adipokine-related diseases. For example, olmesartan, an angiotensin II type 1 (AT1) receptor blocker used to treat hypertension, appears to ameliorate ~~angiotensin II-induced~~ dysregulation of adipokine secretion by reducing ROS and attenuating the expression of NADPH oxidase subunits in adipose tissue (70). This process may directly involve blockade of AT1 receptor because inhibition of angiotensin-converting enzyme by captopril appears to be less effective (70). Another class of medication, metformin, a dimethylbiguanide commonly used as an anti-diabetic agent (71), appears to have an anti-oxidant activity independent of its insulin-sensitizing effects (72). This anti-oxidative function may explain the effects of *in vitro* metformin treatment of adipose tissue ~~in~~ reduc~~ing the~~ mRNA and protein levels of PAI-1 (73), IL-8 (74), and MCP-1 (75). Nevertheless, administration of metformin to subjects with impaired glucose tolerance for 10 weeks does not appear to reduce the mRNA levels of MCP-1 or CD68, a macrophage marker, in adipose tissue (40). Further adipocentric studies are needed to clarify if metformin can regulate the expression and secretion of adipokines *in vivo*, and if this potential effect is mediated by its anti-oxidative mechanisms. Similar potential effects of other anti-oxidative agents and/or supplements (e.g. β-carotene, vitamin E, ascorbate, N-acetylcysteine, etc.) on regulating adipokine expression and secretion need to be evaluated.

Thiazolidinediones. Recent studies highlight the increasingly recognized anti-inflammatory effects of thiazolidinediones (TZDs), peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonists, on adipokine expression and secretion. These widely-used insulin sensitizing agents not only have direct anti-inflammatory effects on adipose tissue (76), but also reduce markers of systemic inflammation, e.g. by decreasing plasma concentrations of CRP and PAI- 1 (77, 78). Exposure of adipocytes or adipose tissue to TZDs ~~results in their~~ reduced secretion of pro-inflammatory adipokines such as PAI-1 (79), IL-6 (80), and IL-8 (74). Thiazolidinediones also reduce TNF-α-mediated transcription of genes encoding pro-inflammatory adipokines in adipocytes, presumably by antagonizing NF-κB transcriptional regulation (81). In contrast, TZDs stimulate the mRNA expression levels of adiponectin and its subsequent secretion into circulation (82). In addition to modulating the expression and secretion of the above adipokines, TZD~~s~~ treatment of ~~subjects~~ with a wide range of BMI also decreases the level of macrophage infiltration in adipose tissue, resulting in improved insulin sensitivity (~~83~~).

The anti-inflammatory effects of TZDs are thought to be mediated, at least in part, through the same mechanism used to achieve their insulin-sensitizing effects, i.e. *via* binding to PPAR-γ (81). Activation of PPAR-γ by troglitazone, a TZD~~s~~ agent, interferes with NF-κB signaling in adipose tissue and downregulates the transcription of pro-inflammatory adipokines (81). In addition, rosiglitazone, another TZD~~s~~ agent, suppresses the induction of MAPK pathway by TNF-α in adipocytes (84). These mechanisms may help explain the

efficacy of abscisic acid, a naturally occurring phytochemical with structural similarities to TZDs, in decreasing TNF-α mRNA levels and macrophage infiltration while stimulating the transcription of adiponectin gene in adipose tissue (85).

Despite their efficacy, TZDs are associated with a number of side effects, e.g. weight gain and congestive heart failure (86). These effects have prompted efforts to search for novel PPAR-γ ligands, such as non-TZDs PPAR-agonists and selective PPAR modulators (86). More studies are needed to determine the potential ability of these ligands to regulate adipokine expression and secretion.

Statins. These agents constitute a different class of medication that may regulate adipokine expression and secretion by exerting anti-inflammatory effects. These potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase are widely used to reduce serum total cholesterol and low-density lipoprotein cholesterol levels and, thus, decrease the incidence of coronary heart disease (87). In addition, cerivastatin has been shown to reduce mRNA and protein levels of IL-6 from adipocytes, presumably through inhibition of the NF-κB pathway (87). Atorvastatin, another statin, directly inhibits gene expression and secretion of IL-6 (88) and TNF-α (89) from adipocytes as well as reduces their circulating concentrations in hypercholesterolemic rabbits.

Other agents. There are other pharmacologic agents that interfere with adipose tissue NF-κB signaling pathway as well as other pro-inflammatory pathways such as MAPK as described above; nevertheless, these agents are not currently used as medications to treat people in clinical settings. Such agents that have been shown to regulate adipokine expression and secretion include sulfasalazine and BAY 11-7082 (90). These agents decrease the release of IL-6, IL-8, and TNF-α from adipose tissue by reducing the protein expression of IKKβ and, thus, the activity of NF-κB DNA binding activity (90). Notably, sulfasalazine, a salicylate derivative, and salicylates have been shown to improve insulin sensitivity and glycemic control in obese rodents (91) and in people with T2DM (92). The side effects of high doses of aspirin, e.g. gastrointestinal bleeding (93), preclude prolonged usage of this medication; thus, current studies focus on the efficacy of other salicylate derivatives in ameliorating insulin resistance. More studies are needed to determine the potential of these derivatives on regulating adipokine expression and secretion. Other pharmacologic agents targeting MAPK pathways also suppress pro-inflammatory adipokine secretion, as exemplified by the ability of SB0025, a specific p38 MAPK inhibitor, to partially reduce mRNA and protein levels of IL-6 and IL-8 in adipose tissue (57). Combination of SB0025 with a specific NF-κB inhibitor, 6-amino-4-phenoxyphenethylaminoquinazoline, inhibits secretion of both adipokines to a greater extent (57). These *in vitro* data indicate the potential to develop pharmacologic agents for clinical use that inhibit the above pro-inflammatory pathways to regulate adipokine expression and secretion. Such agents will help prevent and/or treat obesity-related diseases.

CONCLUSION

Adipokine expression and secretion by adipocytes and other cells of adipose tissue can be regulated by pharmacologic agents with anti-inflammatory activity against molecular and cellular contributors of adipose tissue inflammation. The exact molecular mechanism(s) of these agents in differentially influencing the secretion of pro- *versus* anti-inflammatory adipokines remains to be determined. Development of novel agents in the future that target both transcriptional and secretory pathways in adipose cells may help ameliorate adipokine-associated diseases (50,94,95).

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