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ADIPOPHARMACOLOGY OF INFLAMMATION AND INSULIN RESISTANCE

Victoria Catalán[1], Amaia Rodríguez[1], Sara Becerril[1], Neira Sáinz[1], Javier Gómez-Ambrosi[1] and Gema Frühbeck[1, 2]
[1] Metabolic Research Laboratory, University of Navarra, Pamplona, Spain,
[2] Department of Endocrinology, Clínica Universitaria de Navarra, Pamplona, Spain

Among the rapidly expanding list of factors synthesized and released by white adipose tissue, the range of cytokines, chemokines and other signaling proteins, collectively termed adipokines, are of particular interest to better understand the pathogenesis of low-grade systemic inflammation associated with obesity. An overwhelming body of evidence further links high circulating concentrations of inflammatory biomarkers with the development of insulin resistance and the progression to type 2 diabetes mellitus. The secretory pattern of adipose tissue characteristic of obesity comprises an increase in pro-inflammatory adipokines together with a decrease in adipokines with anti-inflammatory, cardioprotective and insulin sensitizing actions. These molecules exerts local autocrine and paracrine effects on white adipose tissue physiology at the same time as having systemic effects on other organs. A number of factors derived not only from adipocytes but also from infiltrated macrophages and mast cells, which have been shown to accompany morbid adiposity, further contribute to inflammation and insulin resistance. The evolving notion of adipose tissue as an immuno-modulatory organ together with the improving knowledge of how inflammation exerts a (counter)regulatory action on glucose and lipid metabolism are opening up new therapeutic opportunities for applying anti-inflammatory strategies to counterbalance the detrimental consequences of excess adiposity and its comorbidities. ***Biomed Rev 2006; 17: 43-51.***

Key words: adipose tissue, adipokines, atherosclerosis, diabetes, metabolism, obesity

INTRODUCTION

Due to its apparent simplicity white adipose tissue (WAT) has been ignored as an extraordinarily dynamic endocrine organ for decades (1-8). Not surprisingly, WAT functions were initially limited to lipid synthesis and breakdown given that triglycerides constitute up to 85% of adipose tissue mass (8). Thirty years ago the secretory role of WAT was restricted to the release of fatty acids as well as other lipid moieties such as cholesterol, prostaglandins, steroid hormones and retinol (9). Neither cholesterol nor retinol are directly synthesized by adipocytes, but taken up and stored within WAT. On the contrary, adipose fibroblasts harbour the enzymatic machinery

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Correspondence and reprint request to Dr Gema Frühbeck, Department of Endocrinology, Clínica Universitaria de Navarra, Avda. Pío XII, 36, 31008-Pamplona, Spain. Tel.: 34 948 255 400 (ext. 4484), Fax: 34 948 296 500,
E-mail: gfruhbeck@unav.es

necessary for steroid hormone conversion.

The identification that tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine synthesized and released by adipocytes meant a key finding in further establishing the secretory nature of WAT (10). More interestingly, TNF-α expression was reportedly increased in obesity at the same time as a direct role in obesity-linked insulin resistance was set forward (10-12). Clinical studies have also revealed expression of $mRNA^{TNF-\alpha}$ in human adipose tissue, which also closely correlated with hyperinsulinemia showing positive associations with fasting insulin and triglyceride concentrations (2,10,13). Furthermore, $mRNA^{TNF-\alpha}$ expression correlated positively with body adiposity and was shown to decrease in obese subjects after weight loss.

Kennedy (14) originally proposed that circulating signals generated in proportion to body fat stores influence appetite and energy expenditure in a coordinated manner to regulate satiety and body weight. Accordingly, changes in energy balance sufficient to alter body fat stores were supposed to be signaled *via* one or more circulating factors acting in the brain to elicit compensatory changes in order to match energy intake to energy expenditure. A major development of our knowledge of energy balance regulation and adipobiology was triggered by the paradigm-shifting discovery in 1994 of leptin, an adipocyte-specific secretory protein encoded in the *ob* gene (15). Leptin fulfilled the concept of a lipostatic molecule that informs the hypothalamus about the abundance of body fat, thereby allowing feeding behavior, metabolism, and endocrine physiology to be coupled to the nutritional state of the organism (2). Leptin has been shown to play an essential role in food intake regulation based on its capacity of stimulating key anorexigenic pathways composed by the melanocortinergic cascade at the same time as inhibiting orexigenic signals such as neuropeptide tyrosine (NPY), melanin-concentrating hormone, orexin A, *agouti*-related peptide and endocannabinoids (16-18). Since then remarkable progress has been made in the knowledge of leptin as well as in the application of genetics to understand body weight control (19-22).

ADIPOKINES

The multifunctional nature of adipose tissue relies on its ability to secrete (i.e. synthesize, store, and release) a large number of signaling proteins including hormones, growth factors, enzymes, cytokines, chemokines, acute phase proteins, complement factors and matrix proteins, collectively termed adipokines or adipocytokines (1-6,8-10). At the same time WAT expresses receptors for most of these factors, warranting a wide cross-talk at both local and systemic levels in response to metabolic changes or other specific external stimuli. The diversity of secreted molecules includes factors involved in lipid and glucose metabolism such as lipoprotein lipase, apolipoprotein E, cholesteryl ester transfer protein, glucocorticoids, sex steroids, prostaglandins, adipsin, acylation-stimulating protein, leptin, resistin, adiponectin (Acrp30/adipoQ), osteonectin and cathepsins among others. Growth factors include insulin-like growth factor I (IGF-I), nerve growth factor (NGF), macrophage colony-stimulating factor, transforming growth factor-β, vascular endothelial growth factor (VEGF), heparin-binding epidermal growth-like factor, leukemia inhibitory factor, and bone morphogenetic proteins.

By definition, adipocytokines are cytokines produced by adipocytes. Although adipose tissue secretes a variety of factors, not all of them can be contemplated as adipocytokines. Therefore, the term "adipokines" has been coined to include a wider range of proteins secreted by both adipocytes and nonadipocytes of adipose tissue (3,6,8,9). For instance, while leptin, adiponectin and NGF are mainly produced by adipocytes, a large number of cytokines, chemokines and growth factors are mainly produced by cells of stromovascular and tissue matrix fractions of adipose tissue (3). Also produced by adipose tissue cells are the cytokines TNF-α, interleukin-1 (IL-1), IL-6, IL-10, and IL-18, while monocyte chemoattractant protein-1 (MCP-1/CCL2) and IL-8 (CXCL8) belong to the superfamily of chemokines. Such a broad spectrum of adipokines contributes to WAT's pleiotropism as well as underlying its extensive auto-, para- and endocrine activity.

ADIPOKINES LINKED TO INFLAMMATION, IMMUNITY, AND INSULIN RESISTANCE

Today, the adipobiology of inflammation is one of the most pursued fields of research in obesity and related diseases. In this context, TNF-α, IL-1, IL-6, C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, MCP-1, IL-8, plasminogen activator inhibitor-1 (PAI-1), tissue factor, nitric oxide, the molecules of the renin-angiotensin system as well as leptin, adiponectin, resistin, NGF, visfatin, retinol-binding protein 4 (RBP4), and toll-like receptor 4 (TLR4) represent an extraordinarily relevant group of obesigenic, diabetogenic and

atherogenic mediators (3,8,23-41). In fact, parallels between adipocytes and immune cells have been drawn with preadipocytes being able to act like macrophages (35). The figure summarizes the main adipokines involved in the modulation of inflammation exerting either pro-inflammatory actions or conveying anti-inflammatory signals. Since the role of most adipokines has been extensively reviewed elsewhere (1-8,28-43), we will describe below the potential mechanistic basis for the link between inflammation and insulin resistance focusing on some adipokines that have emerged more recently in the pro-inflammatory and metabolic (cardiometabolic) syndrome scenario.

Teleologically, the onset of inflammation in the setting of obesity has not been completely disentangled. Currently, it is not clear whether elevated circulating concentrations of inflammatory factors serve as indicators of systemic inflammation or reflect a spillover of adipose-derived bioactive molecules in response to the hypoxia that takes place as a consequence of adipose mass expansion (8,9). In this context, an increased expression of hypoxia inducible factor-1alpha, a transcription factor that operates as a molecular sensor for low oxygen levels, may play an important role. This factor stimulates the production and subsequent release of inflammatory cytokines, chemokines and angiogenic factors aimed at enhancing blood flow and vascularization of inflamed adipose tissue (44), suggesting the relevance of hypoxic conditions in triggering an inflammatory cascade.

At epidemiological level, an association between inflammatory markers, such as circulating concentrations of fibrinogen and other acute-phase reactants, and obesity or type 2 diabetes mellitus (T2DM) has been identified more than half a century ago (45-47). However, at that time point no causal inferences with T2DM pathogenesis were established. In the last decade, more widespread epidemiological studies have provided additional information on the link between inflammation and insulin resistance (48-53).

Serum amyloid A

Serum amyloid A (SAA) represents an acute-phase reactant protein secreted by diverse cell types, including adipocytes, which has been associated with systemic inflammation at the same time as being linked to atherosclerosis, serving as a predictor of coronary disease and cardiovascular outcome (30). Circulating SAA concentrations are increased in obese and diabetic patients (28, 54). White adipose tissue is known to express low levels of SAA under normal circumstances, which are extraordinarily upregulated in obesity (55). In addition to displacing apolipoprotein A1 from HDL-cholesterol, thereby

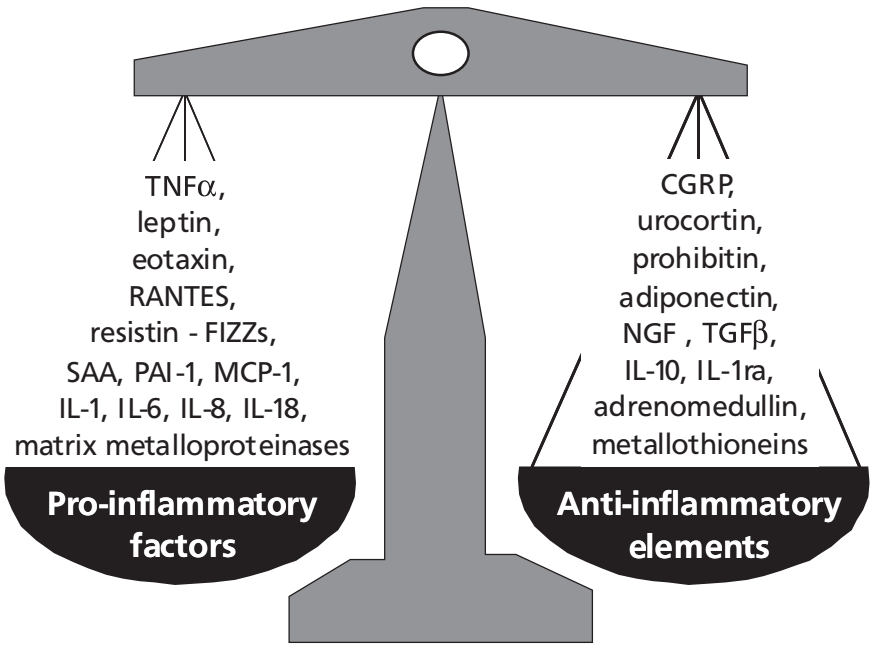

***Figure**. Schematic representation of selected adipokines participating in the development of inflammation.*

increasing its binding to macrophages, SAA further operates as a chemoattractant, a modulator of metalloproteinase activity and a stimulator of T-cell cytokine production (28).

Monocyte chemoattractant protein-1

Monocyte chemoattractant protein-1 (CCL2) like other chemokines plays a relevant role in the recruitment to WAT of monocytes bearing cysteine-cysteine (CC) motif chemokine receptor 2 (CCR2) (56-58); adipose-derived MCP-1 also being related to echocardiographic abnormalities (59). Elevated circulating concentrations of MCP1 have been observed in patients at risk for coronary artery disease (60). Furthermore, myocardial ischemia is known to be associated with an inflammatory response leading to leukocyte recruitment with MCP-1 being directly involved in ventricular remodeling. Recent evidence further supports that MCP-1 contributes to thrombin generation and thrombus formation via tissue factor production (57). Therefore, MCP-1 (CCL2) and CCR2 may turn out as extremely attractive therapeutic targets to counteract vascular disease pathogenesis.

Visfatin

Visfatin is a recently identified adipokine. Its putative anti-diabetic effect is mediated by binding to the insulin receptor and thus exerting an insulino-mimetic effect both *in vitro* and *in vivo* (60-66). Visfatin was originally termed pre-B-cell colony-enhancing factor 1, a cytokine with increased presence in bronchoalveolar lavage fluid of animal models of acute lung injury as well as in neutrophils of septic patients (32). Contrarily to what would be expected given its name, plasma concentrations of visfatin and adipose visfatin mRNA expression have been reported to correlate with measures of obesity but not with visceral fat mass or waist-to-hip ratio. Moreover, no differences in visfatin mRNA expression between visceral and subcutaneous fat depots have been observed (62). Interleukin-6 seems to exert an inhibitory effect on visfatin expression, which is in part mediated by the p44/42 mitogen-activated protein kinase (63). A two-fold increase in circulating concentrations of visfatin in T2DM patients has been recently reported (64). However, the association between visfatin and T2DM disappeared after adjustment for body mass index and waist-to-hip ratio. Up to date, the pathophysiological relevance of visfatin remains unclear and deserves further analysis especially as regards the paradoxical effects of favoring fat accretion and simultaneously promoting insulin sensitivity (65,66). Visfatin may enhance fat accumulation in the intra-abdominal depot, as a feedback control preventing the detrimental effects of increased visceral fat on insulin sensitivity, or merely embody an epiphenomenon with potential useful application as a surrogate marker of increased omental adipose tissue. For further update of visfatin, see the article by Ichi Shimamoto *et al* in this volume of *Biomedical Reviews*.

Retinol-binding protein 4

Studies in mice suggest that adipocytes operate as glucose sensors regulating systemic glucose metabolism through the release of RBP4, a further identified novel adipokine which provides a link between obesity and insulin resistance in rodents (67). These observations have been extended to humans (68), where RBP4 has been found to be elevated in subjects with impaired fasting glucose tolerance or T2DM and to be independently related to sex and fasting plasma glucose concentrations, clinical parameters with known association to insulin resistance (69). However, other researchers have pointed out profound differences between rodents and humans in the regulation of adipose and circulating RBP4 (70). In fact, RBP4 was found to be highly expressed in isolated and mature human adipocytes at the same time as being secreted by differentiating human adipocytes. In contrast to the seminal observations in mice, $mRNA^{RBP4}$ was shown to be downregulated in WAT of obese women with similar circulating RBP4 concentrations in normal weight, overweight and obese patients (70). Retinol binding protein 4 was observed to correlate positively with GLUT4 expression in WAT independently of other obesity-associated variables. Additionally, a modest weight loss of 5% slightly decreased adipose RBP4 expression, but was not accompanied by significant changes in circulating concentrations (70). These findings challenge the notion that glucose uptake by adipocytes plays a dominant role in the regulation of RBP4 in humans.

Toll-like receptor 4

Toll-like receptors play a key role in innate immune response at the same time as operating as inflammatory signals. Toll-like receptor 4 is the receptor for lipopolysaccharide and its stimulation has been shown to activate proinflammatory pathways as well as induce cytokine expression in a variety of cell types. As indicated above, an inflammatory cascade is activated in tissues of obese animals and humans exerting a crucial role in obesity-associated insulin resistance. In this context, circu-

lating fatty acids, which are often increased in obesity, have been observed to activate TLR4 signaling in adipocytes and macrophages (71). Moreover, the ability of fatty acids to induce inflammatory signals in fat cells and macrophages is blunted in the absence of TLR4. Given these circumstances, mice lacking TLR4 are substantially protected from the effects of lipid accumulation leading to the suppression of insulin signaling in muscle as well as to reduction of insulin-mediated changes in systemic glucose metabolism (71). Messenger RNA^{TLR4} levels are reportedly induced during adipocyte differentiation being remarkably enhanced in adipose tissue of obese mice (72). Furthermore, TLR4 activation with either LPS or free fatty acids is able to stimulate NF-κB signaling and expression of inflammatory cytokine genes, such as those for TNF-α and IL-6 in 3T3-L1 adipocytes, leading to insulin resistance (72). Taken together these findings suggest that TLR4 is a molecular link between nutrition, lipids and inflammation and that the innate immune system participates in the regulation of energy balance and insulin resistance in response to changes in the nutritional environment with a probable implication of TLR4 activation in adipocytes in the onset of insulin resistance.

THERAPEUTIC PERSPECTIVES

Some drugs currently available in clinical practice are known to exert anti-inflammatory properties beyond their original major pharmacological target, such as statins of the range of the 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors as well as members of the thiazolidinediones (TZDs) with peroxisome proliferator-activated receptor-gamma (PPARγ) agonism. Beyond their primary beneficial actions on cholesterol and glucose homeostasis, respectively, both potent anti-inflammatory effects. For instance, statins downregulate transcriptional activities of NF-κB, hypoxia inducible factor-1alpha and activator protein (AP-1), thereby reducing the expression of prothrombotic and inflammatory cytokines (72). The anti-inflammatory properties of TZDs seem to be mediated *via* the transrepression of NF-κB and the subsequently triggered decrease in the expression of target genes for cytokines, growth factors, cell proliferation/differentiation and migration. Thiazolidinedione-dependent SUMOylation of PPARγ reportedly targets it to the nuclear receptor corepressor-histone deacetylase-3 complexes on gene promoters of NF-κB and AP-1 (73). On the other hand, TZDs exert an PPARγ-independent anti-inflammatory effect *via* glucocorticoid receptor activation (74). Therefore, the clinical effect of TZDs may rely on the anti-inflammatory properties concurrently impacting on the classical control mechanisms of glucose and lipid metabolism to increase insulin sensitivity, and promote plaque remodeling to improve the cardiovascular state. Moreover, activation of other nuclear receptors such as PPARα, PPARδ and the liver X receptor have also been shown to exert anti-inflammatory effects (75,76).

As recently proposed by Chaldakov *et al* (77), from a mechanistic point of view the main adipopharmacologic targets encompass *(i)* nuclear transcription factors (such as PPARs and sterol regulatory element-binding protein-1), *(ii)* products of the intracellular secretory pathways including adipokines and steroid hormones, *(iii)* adipokine signaling pathways, *(iv)* downstream insulin signaling components, *(v)* uncoupling proteins, *(vi)* lipid droplet-associated proteins (perilipin, adipophilin, caveolin-1) as well as *(vii)* adipose-derived stem cells. Metabotrophic factors such as NGF, brain-derived neurotrophic factor, ciliary neurotrophic factor, adiponectin, metallothioneins, and angiopoietin-like proteins are also appreciated as potential adipopharmacologic targets (41,77-80); apelin and visfatin may also be considered (81).

Other approaches to tackle diabetes as well as diabesity, a co-existence of diabetes and obesity in one subject, have fostered gene-transfer technology aimed at either increasing the expression of well-known anorexigenic peptides like leptin (82-84) or counteracting the orexigenic properties of others, e.g. ghrelin (85-87).

CONCLUSION

Obesity, T2DM and cardiovascular diseases share a common metabolic ground characterized by insulin resistance and a low-grade chronic inflammatory state. We highlighted the potential role of adipokines in the development of inflammation-mediated insulin resistance. Therefore, intervention strategies can include drugs that secondarily alter the inflammatory process. The other side of the coin would consist of pharmacological interventions to treat or prevent insulin resistance and T2DM at the same time as modulating cardiometabolic risks.

The worldwide public health problem posed by the increasing prevalence rates of both obesity and diabetes, offers a potentially huge market for a safe and efficacious drug. However, the limited efficacy and side effects of the few currently approved drugs collides with the epidemiological scenario. The obesity pipeline includes the development of drugs working at central and peripheral levels. More recently, gut-derived

incretins are providing new impetus to the development of anti-obesity drugs (88). However, in order to optimize efficacy and reduce the number and severity of adverse effects (89-91), there is a clear need for obesity-directed pharmacogenetics. In this sense, an alternative perspective consisting in a personalized pharmaco-metabolomic approach, which is sensitive to both genetic and environmental influences in each individual, represents one of the most interesting challenges at which to direct our future efforts. Further adipopharmacologic studies may indeed provide new insights into the therapy of inflammation and related insulin resistance, T2DM and cardiovascular disease.

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