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Adipokines and their Involvement as a Target of New Drugs

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Abstract

Globesity is referred to a global epidemic of obesity, affecting millions of individuals. Molecules released by the enlarged adipose tissue, most of which are pro-inflammatory, have been named adipokines. The present review deals with function, molecular targets and the potential clinical relevance of adipokines. Currently, more than 600 adipokines have been identified, many of them, including leptin, visfatin, resistin as well as Retinol Binding Protein4 may serve as informative markers for metabolic and cardiovascular diseases and play important roles in glucose homeostasis, insulin sensitivity as well as metabolic regulation of energy expenditure. Adiponectin on the contrary exerts anti-inflammatory and insulin sensitizing activity. Adiponectin has additional anti-atherogenic effects and low adiponectin serum concentrations are associated with increased risk for cardiovascular diseases. The understanding of the role of adipokines has provided a wealth of information that has opened great opportunities for new therapeutic advances. Adiponectin may be the most prominent example for the potential use of an adipokine in the treatment of obesity and obesity-associated metabolic diseases. In many studies, administration of recombinant adiponectin results in improved insulin sensitivity, increased insulin secretion and beneficial effects on body weight and hyperglycemia. Up-regulation of adiponectin/adiponectin receptors or enhancing adiponectin receptor function may be an interesting therapeutic strategy for obesity-linked insulin resistance. Moreover, the therapeutic use of combined amylin/leptin agonism (with pramlintide and metreleptin) demonstrated a significant weight-lowering effect in obese subjects. Therefore, adipokines may be clinically relevant either as therapeutic tools or as target in the treatment of obesity related diseases.

Keywords: Adipokines; Adipose tissue; Chronic low grade inflammation; Obesity therapy

Introduction

The economic and social development of industrialized countries are accompanied by changes in lifestyle, more and more sedentary, and changes in eating habits that result in a dramatic increase in obesity. Just from 2008 to 2014 people with obesity increased from 1.4 to 2 billion of adults and these numbers are expected to increase [1].

Obesity is associated with a general dysregulation of metabolic equilibrium. It occurs with insulin resistance, dyslipidemia, impaired regulation of blood pressure (BP ≥ 160/90), hypertriglyceridemia (≥ 150 mg/dl), reduced HDL cholesterol (<35 mg/dl, males, <39 mg/dl, females), central obesity (WHR>0.9, Males, >0.85, females and/or BMI>30), micro albuminuria (AER U-> 20 µg/min or albumin/creatinine ratio > 20 mg/g). The combination of these parameters represents a preclinical condition known as metabolic syndrome, Syndrome X or Reaven's syndrome and represents the most important risk factor for cardiovascular diseases, diabetes, chronic liver disease and cancer [2-4].

In recent years, it has become clear that obesity is characterized by a low-grade systemic inflammatory state, which is a pathological basis for metabolic complications induced by obesity [5], this is shown by a change in the concentration of several mediators called adipokines. These molecules are produced preferentially by white adipose tissue (WAT) and mediate the cross-talk among different organs including brain, liver, heart, skeletal and cardiac muscle communicating the nutritional status. They have both pro-inflammatory and anti-inflammatory activities and when obesity occurs, it is an imbalance in the expression of adipokines that contributes to obesity-related complications.

The causes and mechanisms that induce the inflammatory state associated with obesity are not yet fully known, however, the dysfunction of the adipokine pathways has been recognized as a key etiological factor of diseases induced by obesity. It seems to represent the biochemical link between obesity, inflammation and metabolic syndrome. Furthermore, recent evidence shows that the pro-inflammatory adipokines are central to the initiation of pathophysiological processes related to the excess fat.

The goal of research in this field is the identification of the role of adipokines, their cellular sources and the strategy to regulate their production in order to target obesity and obesity-related pathologies.

Adipose Tissue

Over the past 20 years, there have been great strides in understanding the pathophysiological mechanisms by which obesity induces or amplifies its major adverse consequences. In particular the role of adipose tissue was highlighted, no longer regarded as a tissue with simply trophic and mechanical properties but as an organ with endocrine functions and ability to secrete bioactive molecules. It is now considered a key player in the development of lifestyle-related diseases [6].

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In humans, there are two types of adipose tissue: white and brown adipose tissue. They have different composition and cellular localization and, together, constitute the adipose organ. Deposits of subcutaneous and visceral white adipose tissue constitute most of the adipose organ in the normal adult. The brown adipose tissue is less common and is found in the supraclavicular, laterocervical, paravertebral and mediastinal regions.

The two main types of cells that constitute the adipose tissue are white and brown adipocytes. The white adipocytes have a traditional role in the storage of high-energy molecules, while the brown adipocytes are involved in thermogenesis. In addition to adipocytes, other cell types constitute the white adipose tissue: pre-adipocytes, fibroblasts, vascular cells and immune cells. These cells are the stromal-vascular fraction of adipose tissue. Vascular cells include endothelial as well as smooth muscle cells, which are associated with major blood vessels, necessary for the supply of oxygen and nutrients to the adipocytes. Other active adipose tissue components include macrophages and T cells, which play important roles in determining the immune status of adipose tissue [7,8].

Obesity and Inflammation

In obese subjects the expansion of white adipose tissue takes place, determined by an increase in adipocyte size (hypertrophy) due to the storage of excess triglycerides in lipid droplets [9]. A recent study shows that the increase in fat mass following overfeed may also be due to the increase in the number of adipocytes (hyperplasia), but it occurs only in lower-body subcutaneous fat and not in the upper-body subcutaneous fat [10]. However the expansion of adipose tissue leads to an excessive release of free fatty acids by adipocytes. These molecules, while in normal conditions are transported to other tissues and used as a source of energy, in conditions of obesity enter directly into the liver via the portal circulation and increase the levels of free fatty acids inducing an increase of lipid synthesis, gluconeogenesis and insulin resistance in the liver. High levels of circulating free fatty acids can also cause peripheral insulin resistance in both animals and humans [11,12].

These alterations affect the function of adipose tissue [13-16] and induce changes in the microenvironment that contribute to the recruitment of inflammatory cell leading to a state of chronic low grade inflammation [17,18].

In particular free fatty acids bind to the receptor complex toll-like 4 (TLR4) and stimulate the production of cytokines by macrophages, inducing the inflammation which contributes to the metabolic complications associated with obesity [19,20].

The TLR4 is a member of TLRs, a family of pattern-recognition receptors that play an essential role in the innate immune system by activating the cascade of events leading to the synthesis of inflammatory products [21]. It is the obligatory receptor for bacterial LPS but it plays an additional role into the pathogenesis of endogenous lipid-induced insulin resistance.[19]. The binding to TLRs induces the phosphorylation and the activation of the NFkB complex [22], which in turn activates the transcription of many pro-inflammatory genes encoding cytokines, chemokines, and other effectors of the innate immune response [23].

The metabolically dysfunctional adipose tissue is also characterized by higher number of adipocytes undergoing necrosis, and by macrophages distributed around these dead cells in a crown-like structure [7,24,25].

Normally adipose tissue contains 5-10% of macrophages, but in conditions of obesity, the macrophage infiltration reaches 60%. Macrophages residing in adipose tissue are classified into two distinct subtypes: M1, or classically activated, and M2, or alternatively activated. M1 macrophages secrete pro-inflammatory cytokines such as TNF-α and IL-6, produce NO and reactive oxygen species (ROS), that contribute to obesity-related insulin resistance [26,27]. M2 macrophages produce IL-10, IL-1 receptor antagonist and arginase-1 and have been implicated in tissue remodeling [28], including clearance of dead or dying adipocytes and the recruitment and differentiation of adipocyte progenitors [29].

In normal conditions, the macrophages of WAT express markers of alternatively activated macrophages (M2) and support the adaptive thermogenesis [30] and lipolysis [31]; on the contrary obesity leads to the recruitment and accumulation of M1 or classically activated macrophages, as well as T cells [24,25,32].

The presence of macrophages has provided an explanation for the origin of several cytokines derived from adipose tissue, and has also demonstrated the close relationship with systemic low-grade inflammation that characterizes obesity [7,26]. As a matter of fact, it has been shown that the decrease of macrophage infiltration or macrophage ablation results in decreased secretion of inflammatory cytokines in adipose tissue and in improved insulin sensitivity in diet-fed obese mice [33,34] . In addition, weight loss reduces macrophage infiltration and pro-inflammatory gene expression in adipose tissue of obese subjects [35,36].

Adipokine Secretion from Adipose Tissue

Molecules such as cytokines and hormones, secreted by different cell types that constitute the adipose tissue are collectively called adipokines [37-40]. From a functional point of view, adipokines are polyvalent molecules, which act with paracrine and endocrine activity [41-44]. They play an important role in glucose metabolism, insulin sensitivity, hypertension, cell adhesion, vascular growth and function, adipogenesis and bone morphogenesis, growth, lipid metabolism, regulation of appetite and satiety and other biological processes [2,45]. These molecules are responsible for the cross-talk among adipose tissue, muscles, and adrenal glands and central as well as sympathetic nervous system.

Currently, more than 600 adipokines have been identified [40,46] and the whole system is complex and redundant, i.e. more molecules partly overlap. But from their numerous functions it is evident the importance of their role in many physiological and pathological processes [2,45] (Table 1). Excess adiposity and adipocyte dysfunction contribute to the development of several metabolic diseases through the alteration of lipid and glucose metabolism and the induction of a low-grade chronic inflammation [47,48].

In obesity, adipose tissue generates large amounts of pro-inflammatory factors, including leptin, resistin, retinol-binding protein 4 (RBP4) and nicotinamide phosphoribosyltransferase (NAMPT), while in the healthy adipose tissue anti-inflammatory adipokines, including adiponectin, are preferentially produced (Figure 1). Adipokine may be clinically relevant either as therapeutic tools or as target in the treatment of obesity related diseases.

Leptin

Leptin is a 16-kDa polypeptide structurally related to cytokines [39]. It was discovered in 1994 by Zhang and coll [49]. It is secreted almost exclusively by adipocytes of WAT and communicates the nutritional status to other organs playing an important role in the

	sources	obesity	Principal function	Relevance	References
Leptin	adipocytes	increase	Decreases appetite; improves hypertrigliceridemia and insuln sensitivity	Marker of body fat mass; treatment of lipodystrophy; treatment of genetic leptin deficency	[50,51]
NAMPT/ Visfatin	adipocytes	increase	Improves glucose metabolism	Putative marker of systemic inflammation and atherosclerosis	[64,60]
Resistin	monocytes macrophages	increase	Contributes to systemic inflammation and induces insulin resistance	Putative marker for metabolic disease in humans, particularly type 2 diabetes, myocardial infarct, atherosclerosis	[71,73-79]
Vaspin	Adipocytes macrophages	increase	Improves glucose metabolism; reduces food intake	Possible target for obesity and type 2 diabetes	[80,81,89]
Apelin	Adipocytes macrophages	increase	Improves insulin sensitivity and glucose metabolism	Possible target for obesity and type 2 diabetes	[101,103]
RPB4	adipocytes macrophages	increase	Improve insulin resitance and systemic inflammation	Putative marker of adipose tissue inflammation	[107,115]
Adiponectin	adipocytes	decrease	Insulin sensitizer; anti-inflammatory	Promising candidates for further development as therapeutics for insulin resistance.	[118,119]

Table 1: Sources and function of key adipokines.

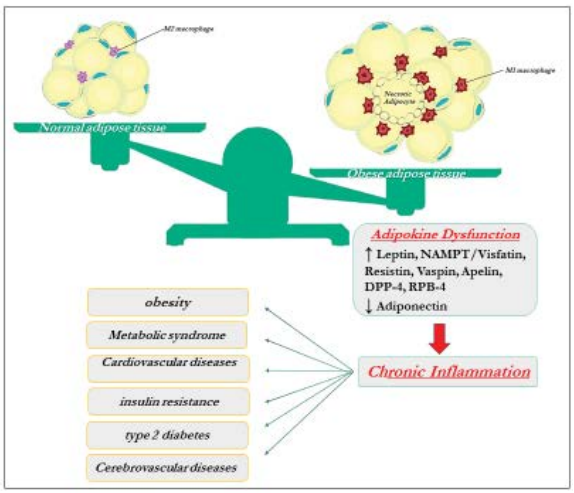

Figure 1: The obese adipose tissue (hyperplastic and hypertrophic) leads to the altered secretion of adipokines that contribute to the recruitment of inflammatory cells and the switch M2-M1. The M1 macrophages are arranged around the necrotic adipocytes in crown-like structures.

All this contributes to chronic inflammation of adipose tissue and finally to the development of obesity-related diseases.

metabolic regulation of satiety, appetite, food intake, activity and energy expenditure [50].

Circulating leptin levels are directly proportional to the amount of body fat, reflecting the status of energy stores. It varies with caloric intake: decreasing in fasting and increasing with food intake. Then increased levels of circulating leptin are found in obese subjects.

The main site of action is arcuate nucleus of the hypothalamus [51]. At this level, leptin act on NPY/AgRP and POMC neurons. NPY and AgRP lead to increased food intake, while POMC synthesize alpha-MSH anorexigenic peptide that activates the melanocortin receptors and decreases the food intake. Then leptin increases POMC mRNA levels while NPY/AgRP are inhibited [51-53].

Leptin has also important effects on glucose homeostasis and hepatic insulin sensitivity which are mediated by suppressing the expression of glucose-6-phosphate and phosphoenolpiruvate kinase [51], that are key enzymes in the fatty acid pathway, and by increasing fatty acid oxidation and decreasing triglyceride storage in muscle by activating AMPK [54].

Recently, it has been highlighted the correlation between high levels of circulating leptin and increased cardiovascular risk. Leptin, in fact, can increase platelet aggregation and arterial thrombosis, promote angiogenesis, impair arterial distensibility and induce proliferation and migration of vascular smooth muscle cells [50,55,56].

Leptin, for its structure similar to cytokines, is also able to modulate the immune system. It acts on macrophages, T-cells and other immune cells to promote the production of pro-inflammatory cytokines such as IL 12 and TNF and inhibit the production of anti-inflammatory cytokines such as IL-4. This probably is one of the causes of chronic inflammation observed in obesity [57].

Nampt/Visfatin

Nicotinamide phosphoribosyltransferase (NAMPT), also known as visfatin and pre-B-cell colony-enhancing factor 1 (PBEF-1) has been described as an adipokine predominantly secreted from visceral WAT [58] with a potential glucose-lowering effect because of its nicotinamide phosphoribosyl transferase activity [58]. This is the rate-limiting enzyme that converts nicotinamide to nicotinamide mononucleotide (NMN) in the salvage pathway of NAD biosynthesis from nicotinamide in humans. Nicotinamide mononucleotide adenylyltransferase 1 converts NMN to NAD [59,60].

However, subsequent studies in humans have also revealed that other tissues and cells can express NAMPT including lymphocytes, bone marrow, muscle, and liver and that the effects of this molecule as an insulin mimetic are controversial [60,61].

Later studies showed that plasma visfatin was related to various metabolic states [62,63]. It was increased in subjects with obesity, type 2 diabetes mellitus, metabolic syndrome and cardiovascular diseases

[64]. Visfatin was initially identified as a novel adipokine with insulin-mimetic properties in mice. Enhanced circulating visfatin/Nampt levels have been reported in metabolic diseases, and their circulating levels correlate with markers of systemic inflammation. In cardiovascular diseases, visfatin/Nampt was initially proposed as a clinical marker of atherosclerosis, endothelial dysfunction, and vascular damage, with a potential prognostic value [65].

Through binding to the insulin receptor, it is able to stimulate the production of IL-6 and MCP-1, important cytokines involved in inflammatory processes. Also it favors the activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) involved in the synthesis of reactive oxygen species, in particular superoxide anion [66,67,60].

Recently it has been demonstrated that hypercaloric feeding as well as aging compromise NAMPT-mediated NAD^+ ($NMN^)$ biosynthesis and may therefore contribute to the pathogenesis of type 2 diabetes [60]. Yoshino et al. recently demonstrated that administration of NMN to mouse models of obesity and type 2 diabetes promotes NAD^+ biosynthesis, thereby ameliorating glucose intolerance and improving hepatic insulin sensitivity [60]. The mechanism by which NAMPT/visfatin contributes to alterations in glucose homeostasis may involve regulation of genes related to oxidative stress, inflammatory response, B cell function [59] and circadian rhythm, at least in part via SIRT1 activation [60,68].

However, further studies are required to understand its physiological functions.

Resistin

In 2001 Steppan and colleagues identified Resistin in a screen for adipocyte genes that are suppressed by insulin-sensitizing drugs in rodents [69]. This adipokine was initially identified as a product of mouse adipose tissue and has been associated with inflammation and insulin resistance. In obese mice the levels of circulating resistin are increased and it was shown that resistin knockout mice on a high-fat diet have improved glucose metabolism. This is due to the activation of suppressor of cytokine signalling 3 (SOCS3), an inhibitor of insulin signalling, in adipocytes [70].

However further analysis in humans have shown that resistin is mainly produced by monocytes and macrophages and not by adipocytes [71]. Mouse and human resistin shares less than 60% identity at the amino acid level [72], but interestingly, human resistin, when expressed in mouse macrophages, also induces insulin resistance [73] suggesting that human and mouse resistin might have similar function despite their molecular differences and different sites of production [74].

Another important aspect is that in human mononuclear cells, transcription of the resistin gene (RETN) is induced by pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α, and Resistin, in turn, increases the expressions of cytokines and adhesion molecules in murine vascular endothelial cells. Another studies showed that in white adipose tissue resistin is inhibited by Rosiglitazone, a agonist, suggesting that the atteuation of RETN transcription mediates the anti-inflammatory effect of rosiglitazone [75].

These studies support the idea that resistin levels may serve as an informative marker for metabolic disease in humans, particularly type 2 diabetes, myocardial infarction, and atherosclerosis [76-79,74]. Future studies are required to investigate the therapeutic potential of resistin inhibition.

Vaspin

Visceral adipose tissue-derived serpin (vaspin), is a member of serine protease inhibitor (SERPIN) family, first identified as a new gene, OL-64, expressed in visceral adipose tissue of Otsuka Long–Evans Tokushima Fatty (OLETF) rats, a model of abdominal obesity and type 2 diabetes [80,81]. Vaspin expression was also found in hypothalamus, stomach and pancreatic islets [82] but is not expressed in the subcutaneous tissue, brown adipose tissue and other not fat tissues.

In humans, the vaspin is expressed in adipose tissue, stomach, liver and pancreas to a greater extent in overweight and obese compared to lean subjects[81]. Furthermore, there is a greater expression in white adipose tissue compared with the subcutaneous adipose tissue in accordance with the data of OLEFT rats [81,82]. Several research groups have found gender differences in serum vaspin. Healthy women have higher serum vaspin than men. These differences develop during puberty [83-85].

Expression of human vaspin in adipose tissue is regulated in a fat depot-specific manner and could be associated with parameters of obesity, insulin resistance, and glucose metabolism. In fact, low levels of vaspin seem to be typical of lean subjects and athletes, while high serum concentrations have been reported in people who are overweight as well as obese subjects with impaired insulin sensitivity.

Due to the significant correlation between vaspin and obesity and related metabolic diseases, studies on vaspin are geared toward a possible therapeutic application.

In mice with high-fat diet induced obesity, vaspin administration improved insulin sensitivity, glucose tolerance and modulated gene expression of candidate genes for insulin resistance [80,86,87].

Although central vaspin administration led to reduced food intake [82,88], the mechanism of action remains unclear. Bluher [89] suggested that vaspin inhibited proteases that degrade molecules with glucose lowering effects as well as anti-orexigenic factors. Vaspin was associated to inhibition of TNF-α induced expression of intercellular adhesion molecule (ICAM) by preventing ROS generation and subsequent activation of NF-kB [90]. Fat mass expansion was associated with increased vaspin expression and its circulating concentration [81,83,91]. In obese subjects, it was shown that serum vaspin decreased following modest weight loss accompanied by improved parameters relevant to insulin resistance [92]. These findings suggested that vaspin may provide a compensatory response to antagonize the action of proteases that could be up regulated in states of insulin resistance [93].

Although these rodent studies suggest vaspin as future pharmacological therapeutic agent anti-obesity and its related metabolic diseases, further molecular targets of vaspin have to be identified to fully understand its mechanism of action.

Apelin

Apelin, a 36 amino-acid peptide endogenous ligand of the G-protein-coupled receptor APJ receptor [94], has been identified in a variety of tissues, including central nervous system with high expression in the hypothalamus, stomach, heart, skeletal muscle, and white adipose tissue [95].

Apelin serum levels were shown to be higher in patients with obesity [96], insulin resistance [97,95] and liver cirrhosis [98]. The correlation with hyperinsulinemia and obesity, suggests that apelin may be another

adipokine mediator of impaired adipose tissue function in obesity [95].

However obesity itself, probably, is not the main determinant of increased plasma apelin, in fact circulating apelin concentration was not significantly correlated to BMI [99,100]. Other factors, such as inflammation and oxidative stress, could explain changes in plasma apelin observed in obesity [101,102]. Thus, increased apelin may be due to metabolic derangements that result from compensatory response to insulin resistance [101].

Peripheral apelin administration in obese insulin-resistant mice improved insulin sensitivity and glucose uptake in skeletal muscle [103,104]. However the treatment with apelin provoked fasted hyperglycemia and decreased insulin sensitivity in experimental models [105].

Overall, data obtained from apelin treatment in different rodent models indicate that reduced adipose tissue apelin expression and serum concentration may contribute to improved insulin sensitivity independently of significant weight loss [106], although the exact mechanism is not yet clear and no data are available in humans.

RBP4

Retinol binding protein 4 (RBP4), secreted primarily by the liver and originally known as the only retinol transporter in blood, was recently identified as an adipokine apparently linked to obesity and its comorbidities in humans, including insulin resistance, T2D, MetS, cardiovascular diseases and inflammation.

The mature adipocytes are the main source of RPP4, together with hepatocytes [107]. The relation of RBP4 to insulin resistance and obesity in human clinical studies remains controversial. It has been reported that plasma RBP4 is increased in subjects with obesity, impaired glucose tolerance, and diabetes mellitus [108,109], but other studies did not support the relation between RBP4 and insulin resistance [110,111].

RBP4 was also positively associated with some Met S components, including hypertriglyceridemia, reduced HDL cholesterol, elevated LDL cholesterol and hyperglycemia. These associations were not materially attenuated by further adjustment of adipokines and oxidative and inflammatory markers.

To date, many human studies have found a strong relationship between RBP4 and triglycerides, in association with insulin resistance or not. A study dealing with obese subjects (Caucasian) with MetS and T2D has confirmed that plasma RBP4 levels are elevated in obese patients and no correlation was observed to IR but rather to triglycerides. This evidence suggests a key role of RBP4 in lipid metabolism and shows that triglycerides are the main independent predictor for determining systemic RBP4 levels, regardless of the degree of insulin resistance.

Moreover, it has been proposed a central role of this adipokine in the hypertriglyceridemia associated with insulin-resistant state [112]. RBP4, a pro-inflammatory adipokine, also plays a role in atherogenesis: RBP4 serum levels were significantly elevated in patients with carotid atherosclerosis and positively associated with its severity [113]. A correlation between RPB4 serum level and cardiovascular risk factors, and its specific role in women as an independent predictor of cardiovascular disease, has been reported [114].

A study of 18 patients with incident fatal or nonfatal IHD (Ischemic Heart Disease) or CVD (Cerebrovascular Disease), compared with 18 matched control subjects showed that circulating RBP4 levels were significantly increased in CVD and decreased in IHD with respect to controls.

RBP4 is secreted by both adipocytes [107] and macrophages [115]. A study of middle-aged and elderly Chinese population, has showed a strong correlation between RBP4 levels and elevated inflammatory markers, including IL-6, MCP-1 and TNF-α and this correlation appears to play an important role in the initiation and development of inflammation in adipose tissue [112].

An unresolved inflammatory response associated with an inhibition of insulin signaling represents a high risk for cardiovascular events. Moreover, RBP4 may regulate lipid homeostasis through a classic mechanism of action (e.g. as a carrier of retinoids, or activation of nuclear receptors), or may induce inflammation though a novel mechanism responsible for a reduction in the size of HDL and a loss of their function.

Adiponectin

Several research groups identified adiponectin almost simultaneously as an abundantly secreted adipokine and referred it as Acrp30 adipoQ, and apM1, until the consensus name 'adiponectin' found widespread acceptance [116-118]. It is a protein secreted by white adipose tissue. Since its discovery, several different functions have been found for adiponectin. There is consensus that adiponectin generally exerts insulin sensitising, anti-inflammatory and anti-apoptotic actions on a number of different cell types [118].

In normal subjects, the mean serum levels of adiponectin are comprised between 5 and 10 μg/ml, under adverse metabolic conditions adiponectin release from adipocytes is down-regulated resulting in reduced circulating levels [118,119]. Furthermore, adiponectin expression and secretion increase upon improved insulin sensitivity and weight loss.

The role of adiponectin as an endogenous insulin sensitizer was discovered using experimental down-regulation of the adiponectin gene in knockout mice. Two independent studies demonstrated impaired insulin sensitivity in adiponectin knockout mice as compared to wild type controls.

On the contrary, mice with transgenic adiponectin overexpression are protected against obesity, diabetes (ob/ob mice) and atherosclerosis (ApoE-deficient mice). The effects of adiponectin on glucose homeostasis may be mediated both by increased insulin sensitivity and secretion. Adiponectin plays a direct role in improving systemic insulin sensitivity and shows a paracrine activity on fat cells and hepatocytes. Adiponectin directly improves insulin sensitivity in that its globular C-terminal fragment reduces glucose levels by increasing fatty acid combustion in myocytes. Potential effects of adiponectin on insulin secretion in α-cells, has been examined in several recent studies. Transgenic ob/ob mice overexpressing the globular domain of adiponectin have increased insulin sensitivity and increased insulin secretion independently of body weight compared to control mice. These results suggest that adiponectin has in addition to its insulin-sensitizing properties, protective effects on α -cells. Adiponectin is able to mitigate the apoptotic effects of either palmitate- or ceramide-induced cell death, an effect that may critically depend on the formation of the downstream conversion product of ceramide, sphingosine-1 phosphate in α -cells *in vitro*. Further *in vivo* studies in C57BL/6 mice demonstrated that systemic adiponectin administration results in increased insulin secretion. Adiponectin has additional anti-atherogenic effects and low adiponectin serum concentrations are associated with increased risk for cardiovascular diseases. Endothelium dependent vasoreactivity is impaired in people with low adiponectin levels, which could contribute to the development of hypertension in visceral obese individuals.

Interestingly, various hormones associated with insulin resistance and obesity including catecholamines, insulin, glucocorticoids, TNF-α and IL-6 down-regulate adiponectin expression and secretion in fat cells *in vitro* [120].

Obesity Therapy

To date, therapies for obesity is based on multidisciplinary approach that includes lifestyle modifications such as hypocalorie diet, increased physical activity and psychological interventions. When changes in lifestyle are not enough to lose weight, pharmacotherapy has to be used. Currently, however, only a few drugs are available for the treatment of obesity per se: Orlistat, Lorcaserin and the combination of Phentermine/Topiramate [121-123].

Orlistat reduces the intestinal digestion of fat by inhibiting pancreatic lipase. Lorcaserin is a selective serotonin 2C receptor agonist that suppresses appetite via stimulation of melanocortin receptor 4. Phentermine is a psychostimulant drug indicated for short-term weight loss in overweight or obese adults. It acts through increasing norepinephrine in the hypothalamus. Phentermine, in association with topiramate, is also used for long-term treatment of obesity. Topiramate is indicated for seizures disorders and the prevention of migraine headaches. The mechanism is not thoroughly understood, although it act on GABA-receptors. Another drug for the treatment of obesity is Rimonabant, a cannabinoid receptor 1 inhibitors that reduces food intake and body weight [122]. Obesity leads to excessive endocannabinoid production by adipocytes, which drives CB (1) in a feed-forward dysfunction. Several CB (1) inverse agonists have been developed for the treatment of obesity, including rimonabant, taranabant, and surinabant. These drugs are efficacious at reducing food intake as well as abdominal adiposity and cardiometabolic risk factors [124]. Studies on the mechanism of action of rimonabant have shown that it blocks endocannabinoid receptors 1 affecting the action of leptin [125]. However this drug on 2008 was removed from the market due to its adverse neuropsychiatric effects. A high percentage of patients treated with rimonabant suffered from depression, anxiety, psychomotor agitation, and sleep disorders. A study reported 2 cases of completed suicide and 74 cases suicidality during treatment with rimonabant. All these drugs are accompanied by significant side effects and provide only limited long-term success. In fact, the majority of people who lose weight regain it within 1 year, and almost all within 5 years [126]. Regarding the weight loss, bariatric surgery is much more effective, such as Roux-en-Y bypass or gastric banding, [127,128] but the use is restricted to subjects with severe obesity and is hampered by surgical complications and by the frequent need for reintervention [129].

More often obese patients require drugs for the treatment of obesity-related diseases such as diabetes and hypertension even if the first line of treatment for these diseases is the weight loss. The failure of current therapies could be due to the fact that the pathogenetic factors that affect energy intake, expenditure metabolism cannot be directly targeted [127,130].

The understanding of the role of adipokines have provided a wealth of information that have opened great opportunities for new therapeutic advances. Numerous clinical studies have shown that many drugs used in therapy modulate the secretion of adipokines. To name a few, the PPAR- α agonists which are used for the treatment of type 2 diabetes, increase the secretion of adiponectin, whereas they reduce the expression of resistin [131,132]. Statins, HMG-CoA reductase inhibitor, used for the treatment of dyslipidemia, determine an increased secretion of adiponectin and reduce the levels of IL-6 [133,134]. Patients treated with atorvastatin show reduced levels of leptin [135].

Insulin-sensitizing thiazolidinediones (TZD) probably mediate part of their effect via adiponectin since they increase plasma concentrations of this adipokine in both subjects with normal insulin sensitivity and type 2 diabetes [118]. In contrast, various hormones associated with insulin resistance and obesity including catecholamines, insulin, glucocorticoids, TNF- α and IL-6 downregulate adiponectin expression and secretion in fat cells in vitro [120].

Furthermore it is to be underlined that a modulation of adipokine levels is obtained with the improvement of lifestyle [136]. The beneficial effect of physical activity is mainly due to the reduction of oxidative stress and improvement of adrenergic receptor signaling.

Physical exercise, in particular, promotes the oxidation of fatty acids by reducing insulin resistance constant aerobic exercise induces a decrease of adipokines and inflammatory cytokines (CRP, TNFalpha, IL-6) and increases IL-10 and adiponectin.

The majority of the studies on adipokine, since its discovery to date, are directed to the understanding their possible application in treatments of obesity and metabolic disorders [46,137,138]. In this connection, the most intensively studied adipokines have been leptin and adiponectin.

Leptin

Leptin promotes weight loss in obese congenitally leptin-deficient mice [137] and humans [138], but in diet-induced obesity both in rodents and humans [139], leptin has only little weight loss efficacy. Moreover, treatment with higher doses of native leptin or leptin analogs with sustained pharmacokinetics failed to enhance weight loss and increased adverse effects [140].

In 20 years of intensive research, it has been seen that the exogenous administration of leptin in obese individuals does not significantly affect the body weight, neither reduces food intake, nor improves hyperglycemia [50,140]. This is accompanied by paradoxical increase in circulating leptin levels in obese subjects secondary to the development of central leptin resistance [141] due to impaired leptin transport across the BBB and/or impaired leptin signal transduction in neurons [51].

At present, despite difficulties, recombinant leptin and the analogue metreleptin are available for the treatment of congenital leptin deficiency and lipodystrophy in Japan and in the USA [46,142]. Metreleptin is used also for the treatment of diabetes and/or hypertriglyceridemia, in patients with rare forms of congenital lipodistrophy [143] and has been suggested also for the treatment of rabson-mendenhall syndrome [144,145]. Several leptin analogs have been designed to increase its potency and lead to enhanced weight loss in high fat diet fed mice [146].

Recent findings suggested that amylin, a pancreatic α -cell-derived hormone, is able to restore leptin sensitivity and when used in combination with leptin to enhance body weight loss in obese rodents and humans [147]. This therapeutic use of combined amylin/leptin agonism (with pramlintide and metreleptin) demonstrated a significant weight-lowering effect in obese subjects. However, the latest randomized clinical trial on pramlintide/metreleptin as novel strategy in obesity treatment has been recently stopped because of significant problems with antibody generation and skin reactions.

In summary, even if the mechanism of action of leptin is well established and the treatment concept has been successfully proven in rodent models, an efficacious and safe treatment of human diseases is

not guaranteed.

Adiponectin

Adiponectin may be the most prominent example for the potential use of an adipokine in the treatment of obesity and obesity-associated metabolic diseases. In many studies, administration of recombinant adiponectin results in improved (hepatic) insulin sensitivity, increased insulin secretion [148] and beneficial effects on body weight and hyperglycemia118. Adiponectin exerts insulin-sensitizing effects through binding to its receptors, leading to activation of AMPK, PPAR-α, and potentially other unknown molecular pathways [149]. In obesity-linked insulin resistance, both adiponectin and adiponectin receptors are down regulated, leading to activation of signaling pathways involved in metabolism regulation. Up-regulation of adiponectin/adiponectin receptors or enhancing adiponectin receptor function may be an interesting therapeutic strategy for obesity-linked insulin resistance [41].

In a recent study, no effect of recombinant adiponectin on glucose levels, HbA1c, plasma lipids or body weight has been found [150]. However, this failure to lower blood glucose in animal models of type 2 diabetes could be due to ineffective recombinant adiponectin preparations [150]. Very recently, Okada-Iwabu and coworkers reported the production of an orally active, synthetic small-molecule adiponectin receptor agonist that they have termed AdipoRon. This molecule binds to adiponectin receptors and ameliorates insulin resistance and glucose intolerance in mice. Importantly, AdipoRon ameliorates diabetes and prolonges lifespan of *db*/*db* mice on a high-fat diet [151,152]. Taken together, adiponectin or adiponectin receptor agonists are promising candidates for further development as therapeutics for insulin resistance.

In 2013 Chen analyzed the molecular interaction network of adiponectin and the topological properties of these network through Hub Object Analyzer (Hubba) an open sources software [149]. The Hubba method facilitates the elucidation of adiponectin related signaling pathway and will be helpful for the identification of key signaling molecules, but more efforts are required to distinguish between functional and non-functional protein-protein interactions.

Conclusion

Obesity and its complications have reached epidemic proportions and raised the need to develop new pharmacological treatments. It is very important to find new drugs which target the mechanisms underlying the pathogenesis of obesity and the rational manipulation of adipokines is becoming a promising approach for the therapies of obesity and associated metabolic diseases.

Most adipokines may be involved in the etiopathogenesis of metabolic syndrome and are certainly useful predictive and prognostic biochemical markers. However, further studies are needed to elucidate their possible use in therapies for obesity, and to adopt a strategy to rebalance their production.

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