Adiponectin normalization: a clue to the anti-metabolic syndrome action of rimonabant

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Obesity, currently associated with metabolic syndrome is characterized by an excessive fat storage in different organs, in particular adipose tissue, inducing the loss of its structural and functional integrity. Being aware of the importance of adipose tissue endocrine function and the key role of adipocytokines, such as adiponectin, in obesity and metabolic syndrome drives the necessity to develop new drugs that can exert a specific action on adipose tissue and on adiponectin levels. Rimonabant, an antiobesity drug, presents a dual effect by decreasing food intake and importantly increasing adiponectin. This review focuses on the key role of adiponectin regulation in the success of rimonabant and suggests that this adipohormone may be considered as a therapeutic target to design innovative and promising antiobesity and anti-metabolic syndrome drugs.

Obesity and associated metabolic syndrome: the curse of the 21st century

Obesity is a worldwide health problem, particularly in rich and industrialized countries which allow consumption devoid of limits and rules. Today obese people represent a third of Americans and a fifth of Europeans and this pandemic affects more children every year [1].

The seriousness of obesity depends on its associated metabolic disorders that strongly increase the risk of cardiovascular diseases [2]. Obesity is a metabolic disease currently associated with a cluster of chronic and progressive pathologies presenting several features of metabolic syndrome, including type 2 diabetes, hyperinsulinemia and insulin resistance, dyslipidemia, atherosclerosis, hypertension, steatohepatitis, inflammation and cancer [3,4]. The excessive fat accumulation in principal organs and tissues involved in energy metabolism regulation, such as adipose tissue, liver and muscle, impairs tissue integrity and causes a confined inflammation characterized by an increase in the proinflammatory cytokines such as tumor necrosis factor α (TNFα) [5]. This local inflammation may play a key part in the development of insulin resistance in these tissues. The increase in TNFα level could induce, in its turn, insulin resistance, probably by saturating the insulin-signaling pathway [6,7]. Insulin resistance reduces fatty acid oxidation, markedly amplifies the pathological excessive fat storage and gives a chronic and progressive nature to this process. Obesity is also characterized by a whole inflammatory state [2] with an increase in circulating level of proinflammatory cytokines such as TNFα, C-reactive protein (CRP), interleukin-1-β (IL-1β), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), transforming growth factor β (TGFβ), and a decrease in anti-inflammatory cytokine levels such as adiponectin [8]. This obesity-associated inflammatory component seems to play an important part in the dramatic progression of obesity and metabolic syndrome [5]. In addition, metabolic dysfunction of the principal organs involved in lipid and glucose metabolism is connected with a whole body lipid disturbance called dyslipidemia: characterized by an increase in circulating levels of cholesterol, triglycerides and free fatty acids, and by the reduction in the ratio of circulating levels of high-density lipoprotein-cholesterol (HDLc) and low-density lipoprotein-cholesterol (LDLc) [9]. Dyslipidemia is closely related to an increased risk of cardiovascular diseases including atherosclerosis, hypertension and myocardial infraction. The relationship

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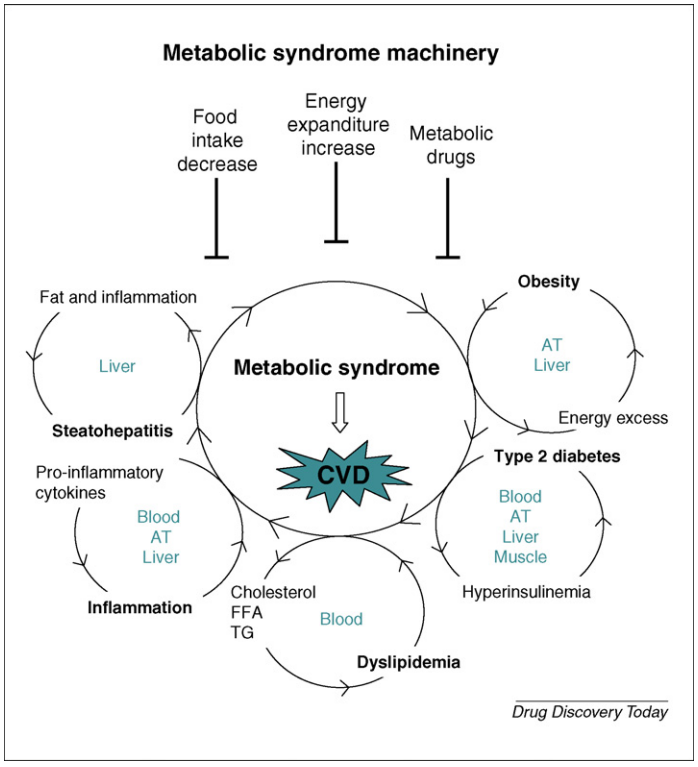

FIGURE 1

Metabolic syndrome machinery. In this simplified scheme, obesity, type 2 diabetes, dyslipidemia, inflammation and steatohepatitis are represented as cycles that supply metabolic syndrome inducing the development of cardiovascular disorders (CVDs). Each cycle of a metabolic disorder is induced by a main dysregulation, such as energy excess, hyperinsulinemia, cholesterol, free fatty acids (FFAs) and triglycerides (TGs), proinflammatory cytokines, fat and inflammation. Inside the cycles, the principal organs or tissues involved in these pathologies supplying metabolic syndrome are enounced: blood, adipose tissue (AT), liver and muscle. In addition, food intake decrease, energy expenditure increase and drugs acting on energy metabolism are represented as the inhibitors of metabolic syndrome progression.

between each main disorder and the metabolic syndrome is represented in Fig. 1, where obesity, type 2 diabetes, dyslipidemia, inflammation and steatohepatitis supply this machinery leading to the increased risk of cardiovascular disorders.

On the basis of these observations, it is clear that the structural and functional integrity of organs and tissues, such as adipose tissue, which are involved in the regulation of lipid and glucose metabolism and in the maintenance of energy homeostasis, plays a crucial role in the pathophysiological processes of obesity and associated metabolic diseases as are seen clustered in metabolic syndrome. Pharmacotherapy targeting the restoration of structural and functional integrity of adipose tissue (and related tissues and organs as indicated above) may represent promising pathways in the treatment of obesity and metabolic syndrome. This review highlights the involvement of adipose tissue integrity and adiponectin regulation in the success of antiobesity and anti-metabolic syndrome drugs such as rimonabant.

Pathophysiological role of adipose tissue

Adipose tissue has a highly specialized function of fat accumulation in situation of energy intake overload that can be used during periods of high-energy consumption or food deprivation. This tissue is mainly composed by adipose cells (adipocytes) at different states of differentiation including adipoblasts, preadipocytes, immature and mature adipocytes [10,11]. Cellular distribution and relative abundance of each cellular subtype confer the heterogeneity characterizing this tissue, which is under hormonal and nutritional control. In pathological conditions, excessive adipose tissue development depends on hyperplasia (increase in several adipocytes by cell proliferation associated with the recruitment of new adipose cells from precursors) and hypertrophy (increase in adipocyte size because of fat storage). Hypertrophy and hyperplasia induce a loss of adipose tissue heterogeneity associated with a dramatic disturbance to its structure and function [12].

This endocrine tissue is able to express and secrete numerous molecules and biologically active proteins called adipocytokines or adipokines including leptin, TNFα, IL-6, IL-1β, PAI-1, TGFβ, angiotensinogen, adipsin, resistin, acylation-stimulating protein (ASP) and adiponectin [13–15]. Through auto-, para- and endocrine mechanisms these adipocytokines (growth factors, hormones and cytokines) play multiple and important roles not only in several pathophysiological processes, particularly those involved in the regulation of energy metabolism and body weight homeostasis [16,17], but also in vascular, immune and reproductive systems [14]. The expression and secretion profile of these adipocytokines reflect the state of adipose tissue. The loss of adipose tissue heterogeneity is associated with the dysregulation in its endocrine function, enzyme activities and with the loss of its response to hormonal regulator, such as insulin, leading to insulin resistance that plays a crucial role in the development and progression of obesity and associated metabolic diseases.

These observations suggest that therapeutic strategy leading to the restoration of adipose tissue integrity (structural heterogeneity and endocrine function) may be a promising pathway in obesity and metabolic syndrome treatment.

Adiponectin regulation as a target for obesity and metabolic syndrome treatment

Adiponectin or adipocyte complement-related protein (Acrp30 – also known as AdipoQ, ApM1 and GBP28), originally identified by four independent groups, is a 30-kDa adipocytokine exclusively expressed and secreted by adipose tissue [18–21]. It has been shown to regulate lipid and glucose metabolism and to play a key role in body weight regulation and homeostasis. Adiponectin has also been reported to be directly involved in several metabolic diseases such as obesity and associated complications including diabetes, hyperinsulinemia and insulin resistance, dyslipidemia, hypertension, hepatic pathologies and inflammation [22]. These pathologies represent the principal features of metabolic syndrome that significantly increase the risk of cardiovascular diseases. Today, adiponectin is considered as a biomarker of metabolic syndrome and associated complications [23].

Adiponectin and obesity, diabetes and insulin resistance

Experimental and clinical studies have shown that adipose tissue expression and plasma levels of adiponectin are decreased in obese and type 2 diabetes subjects. The low plasma levels of adiponectin have been proposed to be a predictor for the development of insulin resistance and diabetes [24]. Furthermore, in animal models of

obesity and diabetes, adiponectin treatment reduced body weight, improved hyperglycemia, ameliorated hyperinsulinemia and insulin resistance, and increased fatty acid oxidation and lipid clearance to improve the whole lipid profile significantly [25–28]. These data confer to the adiponectin an important role in the regulation of lipid and glucose metabolism homeostasis as well as antiobesity, antidiabetes and insulin-sensitizing properties.

Adiponectin and inflammation

Metabolic diseases such as obesity and diabetes are currently associated with a progressive low-grade state of inflammation characterized by an increase in plasma and tissue (liver, muscle and adipose tissue) levels of proinflammatory cytokines [29]. Several studies in animal models and humans, have reported that adiponectin plasma levels are inversely correlated with the increase in proinflammatory cytokines and markers such as CRP [30]. Moreover, mice lacking adiponectin present a chronic inflammatory state associated with a strong increase in proinflammatory plasma levels, in particular the TNFα [31,32]. Treatment of these mice with adiponectin fully reverses this inflammation by reducing tissue and plasma levels of proinflammatory cytokines [33]. This anti-inflammatory activity of adiponectin may originate in the negative correlation between adiponectin and TNFα [31]. Adiponectin and TNFα antagonize each other in their target tissues, particularly in adipose tissue where the reduction of adiponectin expression is associated with the increase in proinflammatory cytokines underlining an inflammatory state of adipose tissue, which may progress and induce insulin resistance in this tissue [6,7]. Inflammation and insulin resistance in adipose tissue could lead to inflammation and insulin resistance in other organs and tissues, such as liver and muscle, and to the appearance of serious pathologies as dyslipidemia, hepatic diseases and cardiovascular disorders [34].

Adiponectin and steatohepatitis

Hepatic steatosis, characterized by fat accumulation in liver, is a major metabolic complication associated with obesity and metabolic syndrome [35,36]. Steatohepatitis is the inflammatory state of this pathology characterized by an increase in tissue and plasma levels of proinflammatory cytokines such as TNFα, which is probably responsible for the progression to fibrosis and cirrhosis [33,36]. Fat accumulation in liver is reflected in a hepatic disorder in lipid and glucose metabolism, which could be due in large part to the increased TNFα levels and insulin resistance. The reduction of the adiponectin plasma level is correlated to hepatic steatosis [23,37]. Adiponectin treatment of animal models abolishes steatohepatitis by reducing hepatomegaly and fat accumulation in liver, as well as plasma levels of liver feature markers such as amino-transferases [38]. Adiponectin could exert its hepato-protective role by reducing TNFα hepatic and plasma levels [38,39], by reducing hyperinsulinemia and increasing insulin sensitivity of liver. In addition, adiponectin could improve steatohepatitis by inhibiting enzyme activity involved in fatty acid metabolism and by increasing free fatty acid oxidation in muscle and liver [38,40].

Adiponectin, dyslipidemia and cardiovascular diseases

Overweight, obesity and associated metabolic disorders, clustered in metabolic syndrome, increase the risk of developping cardiovascular diseases which include hypertension, coronary atherosclerotic disease and congestive heart failure [41]. All these pathologies are closely associated with an atherogenic dyslipidemia that is a causal factor in cardiovascular disease.

Dyslipidemia is characterized by elevated triglycerides, cholesterol, low high-density lipoprotein and small dense low-density lipoprotein particles [42]. The circulating rate of adiponectin is inversely correlated to plasma levels of triglycerides, cholesterol and free fatty acids [43]. It is well established that dysregulation in adipocytokine levels may affect cardiovascular risk factors. The treatment with adiponectin reduces plasma levels of these parameters suggesting an important role of this hormone in lipid and glucose metabolism, and the involvement of its dysregulation on metabolic disorders associated with dyslipidemia [38]. This hormone induces the maintenance of functional integrity of endothelial cells and inhibits the proliferation of smooth muscle cells, notably in vascular remodeling processes [44]. Adiponectin also exerts an antihypertrophic action and protects against ischemic heart disease by a mechanism involving AMPK pathway [44]. In addition, a low adiponectin serum level is strictly connected with hypertension, suggesting that hypoadiponectinemia could be considered as a predictor biomarker for cardiovascular diseases, while high levels of adiponectin are protective [45].

These findings indicate that adiponectin has a cardio-protective role, which may be mediated by its antiatherosclerosis, antithrombosis, antihypertension, anti-inflammatory and antidyslipidemic effects [44,45].

A link between cannabinoid system, obesity and associated metabolic diseases

Cannabinoid system, food intake and body weight

The delta-9-tetrahydrocannabinol (Δ^9-THC), the principal psychoactive component of marijuana or *Cannabis sativa*, has been reported to stimulate food intake with a preference for palatable food high in fat and glucose [46]. The endogenous homologues of Δ^9-THC, called endocannabinoids: anandamide or arachidonoyl ethanolamide (AEA) and 2-arachidonoyl glycerol (2-AG), are lipidic neurotransmitters able to reproduce Δ^9-THC effects on food intake. These neurotransmitters (AEA and 2-AG) are produced in the principal satiety center (hypothalamus) and their levels are higher in obese than in lean animals. Synthetic cannabinoids (WIN 55,212-2 and CP 55,940) can also reproduce the main effects of Δ^9-THC and endocannabinoids *in vitro* and *in vivo* [46].

Cannabinoids (endogenous, exogenous and synthetic) exert their pharmacological activities after interaction with two receptor subtypes: type 1 (CB_1-R) and type 2 (CB_2-R) cannabinoid receptors [47]. CB_1-R have been firstly described in hypothalamic neurons that expressed several neuropeptides involved in food intake and body weight regulation, such as neuropeptide Y, cocaine amphetamine regulated transcription (CART), corticotropin-releasing hormone (CRH), melanin-concentrating hormone (MCH) and orexin [48].

SR141716 (rimonabant), a specific antagonist of CB_1-R, reduces food intake by blocking orexigenic effects of cannabinoids, probably by an antagonist activity on an endogenous cannabinoid tone in hypothalamus. In addition, knockout mice for CB_1-R (CB_1-R KO) eat less and have a lower weight than their wild-type littermates [49].

We have reported that rimonabant reduced food intake and body weight in genetically obese Zucker (fa/fa) rats [50]; however, according to the time course of rimonabant treatment, there is discordance between food intake and body weight reduction. Indeed, body weight loss induced by rimonabant comprises two phases. The early phase is principally food-intake-regulation-dependent: during the first days of treatment, rimonabant reduced food intake and body weight. This body weight loss induced by rimonabant probably originates from the decrease of food intake, which may be mediated by a mechanism involving the regulation of the expression and release of hypothalamic neuropeptides implicated in the control of both appetite and body weight (i.e. a central effect of rimonabant) [49]. The second phase is food-intake-regulation-independent: after the early phase (4 days of treatment) and throughout the entire period of treatment, rimonabant-induced body weight loss was maintained, whereas food intake increased. These observations suggest the involvement of metabolic and energy expenditure regulation in long-term antiobesity effects of rimonabant treatment, as recently confirmed in human clinical trials [51].

Adiponectin involvement in the antiobesity effects of rimonabant

Intravenous injections of adiponectin induce body weight decrease in obese animals in a food-intake-independent manner [25], and the effect of rimonabant on adiponectin mRNA expression in adipose tissue was investigated. We showed that rimonabant treatment stimulated adiponectin mRNA expression in adipose tissue of obese Zucker (fa/fa) rats. This stimulation was also found in cultured mouse adipocytes and was followed by an increase in adiponectin protein level. We then provided evidence that rat adipose tissue and cultured mouse adipocytes express CB_1-R. Importantly, adipose tissue of obese Zucker (fa/fa) rats overexpresses CB_1-R. We have also shown that rimonabant had no effect on adiponectin expression in adipose tissue of CB_1-R KO mice. These results demonstrated that rimonabant regulates adiponectin expression in adipocytes through a CB_1-R-mediated pathway. These results strongly suggest a role for adipose tissue CB_1-R in the control of body weight homeostasis.

Hyperinsulinemia and insulin resistance are commonly associated with obesity and adiponectin plasma levels decrease [24–28]. We have shown that rimonabant treatment decreased the hyperinsulinemia characterizing obese Zucker (fa/fa) rats. This effect may be mediated at least in part by the up-regulation of adiponectin. The hyperinsulinemia reduction may participate in the overall antiobesity actions of rimonabant.

Our data demonstrated that rimonabant regulated hormones implicated in lipid and glucose metabolism, by a mechanism involving a metabolic 'peripheral' action in addition to its known 'central' effect on food intake and revealed that adiponectin regulation probably played a key role in antiobesity activities of rimonabant.

CB_1-R antagonism inhibits preadipocyte proliferation

In obesity, the excessive fat storage induces marked changes in cellular composition and distribution of adipose tissue with alteration of its endocrine function. We have demonstrated that CB_1-R blocking inhibited cell proliferation of cultured mouse preadipocytes accompanied by a rapid decrease in p42/44 MAP kinase activity [52]. Rimonabant also acted on endocrine function and enzyme content of cultured mouse preadipocytes, as shown by the increase in the expression of two late markers of adipocyte cell maturation such as adiponectin and glyceraldehyde-3-phosphate-dehydrogenase (GAPDH). Surprisingly, this regulation was not followed by morphological changes characteristic of adipocyte differentiation such as lipid accumulation, even if arrested adipocyte cell proliferation was generally followed by fat accumulation [13].

Our hypothesis is that, in this cellular model, rimonabant inhibits preadipocyte cell proliferation and induces an uncoupling of the association between the inhibition of proliferation and lipid accumulation. Although complementary research is needed to clarify this atypical property, the inhibition of preadipocyte cell proliferation and the induction of adipocyte late 'maturation' marker without fat accumulation may participate in the antiobesity effects of rimonabant, particularly in the reduction of fat mass and in the restoration of adipose tissue structure and endocrine function.

CB_1-R antagonism improves metabolic syndrome features

Recently, we displayed food-intake-reduction-independent effects of rimonabant on hepatic steatosis and associated metabolic

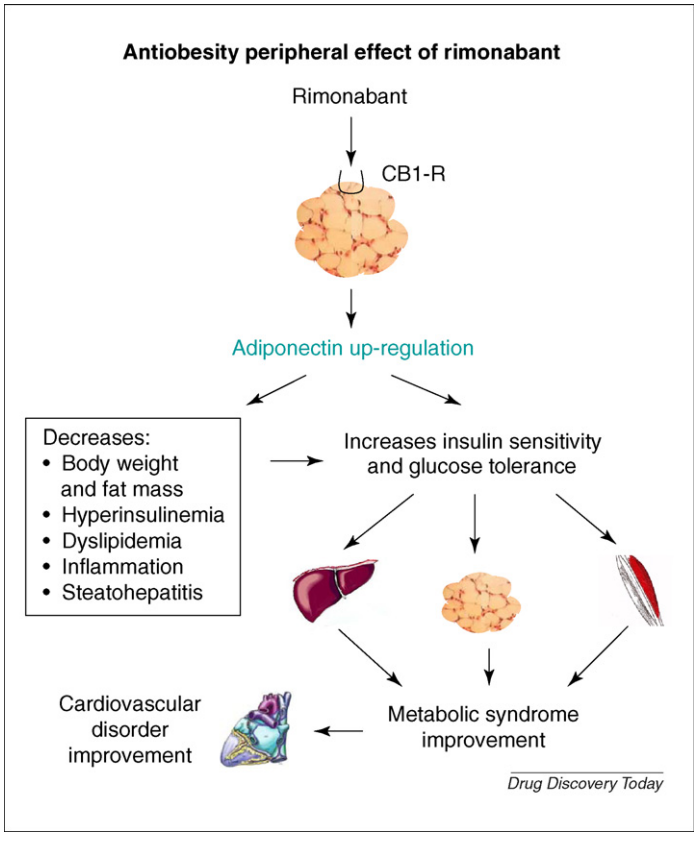

FIGURE 2

Antiobesity peripheral action of rimonabant. By acting directly on type 1 cannabinoid receptors (CB1-Rs) of adipose tissue, rimonabant increases adiponectin level, which decreases body weight and fat mass, hyperinsulinemia, dyslipidemia, inflammation and steatohepatitis. In addition adiponectin improves insulin sensitivity and glucose tolerance of several tissues and organs involved in lipid and glucose metabolism, such as liver, adipose tissue and muscle, that are at the origin of metabolic syndrome improvement inducing a decrease in cardiovascular risk factor.

syndrome features (inflammation, dyslipidemia and low plasma levels of adiponectin) in obese Zucker (fa/fa) rats [53]. Our results showed that rimonabant treatment reduced hepatomegaly, completely abolished hepatic steatosis (fatty liver) and decreased plasma levels of enzyme markers of liver damage (ALT, GGT and ALP). Interestingly, rimonabant treatment strongly reduced elevated levels of hepatic TNFα that characterize the inflammatory state of fatty liver: steatohepatitis [54]. Elevated levels of hepatic proinflammatory cytokines, such as TNFα, were suggested to induce insulin resistance in liver and to be involved in the progression of steatohepatitis to hepatic fibrosis and cirrhosis [36,54]. Rimonabant also reduces elevated plasma levels of TNFα characterizing chronic systemic low-grade inflammation associated with obesity and metabolic diseases [55]. This reduction of plasma and hepatic TNFα levels by rimonabant is probably involved in the reversion of hepatic steatosis and may arrest or prevent the progression of steatohepatitis into fibrosis and cirrhosis and suggest an anti-inflammatory activity of rimonabant. These data reveal that rimonabant possesses a hepato-protective activity, and suggest a new therapeutic role of this CB_1-R antagonist in hepatic diseases [53,56]. Moreover, the steatohepatitis resistance in CB_1-R knockout (CB_1-R KO) mice confirms the proposed role of endocannabinoid system in liver diseases [57].

Furthermore, we have reported that rimonabant treatment improves dyslipidemia, a principal biochemical disorder leading to cardiovascular complications, by reducing plasma levels of cholesterol, free fatty acids and triglycerides, and importantly by increasing the HDLc/LDLc ratio [53]. These results, obtained in animal models, were also found in human clinical trials [58,59]. In addition, rimonabant treatment of obese (fa/fa) rats increased and normalized plasma levels of adiponectin. So the improvement by rimonabant of obesity-associated metabolic diseases could be due in a large part to the increase and the normalization of adiponectin and adipose tissue secretory function restoration and suggests a potential clinical application for this CB_1-R antagonist in the treatment of liver diseases associated with obesity and metabolic syndrome.

Conclusion

All together these observations demonstrate that the loss of adipose tissue integrity appears as a major event leading to the development of metabolic disorders constituting metabolic syndrome. Indeed, hypertrophy and hyperplasia of adipose tissue is generally associated with insulin resistance and inflammation in this tissue and in other tissues and organs involved in energy metabolism such as muscle and liver. The overdevelopment of adipose tissue could also lead to fat accumulation in different organs engendering among others hepatic steatosis and dyslipidemia. In addition, the regulation of a hormone exclusively produced and secreted by adipose tissue, such as adiponectin, seems to play a crucial role in obesity and associated diseases. Several studies have demonstrated that the success of rimonabant treatment was due in a large part to its peripheral effect at adipose tissue, and particularly to the regulation of adiponectin expression and plasma levels (Fig. 2). The multiprotective effects of rimonabant may be mediated by an increase in protective cytokines or hormones such as adiponectin, which is able to improve disorders involved in the metabolic syndrome such as obesity, diabetes and insulin resistance, inflammation, steatohepatitis, dyslipidemia and cardiovascular disorders. Therefore, the development of new drugs exerting a specific action on adipose tissue to restore its integrity and regulate the adiponectin level should be an original and a promising therapeutic axis to significantly improve parameters of metabolic syndrome.

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