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Roles of oxidative stress, adiponectin, and nuclear hormone receptors in obesity-associated insulin resistance and cardiovascular risk

Abstract: Obesity leads to the development of type 2 diabetes mellitus, which is a strong risk factor for cardiovascular disease. A better understanding of the molecular basis of obesity will lead to the establishment of effective prevention strategies for cardiovascular diseases. Adipocytes have been shown to generate a variety of endocrine factors termed adipokines/adipocytokines. Obesity-associated changes to these adipocytokines contribute to the development of cardiovascular diseases. Adiponectin, which is one of the most well-characterized adipocytokines, is produced exclusively by adipocytes and exerts insulin-sensitizing and anti-atherogenic effects. Obese subjects have lower levels of circulating adiponectin, and this is recognized as one of the factors involved in obesity-induced insulin resistance and atherosclerosis. Another pathophysiological feature of obesity may involve the low-grade chronic inflammation in adipose tissue. This inflammatory process increases oxidative stress in adipose tissue, which may affect remote organs, leading to the development of diabetes, hypertension, and atherosclerosis. Nuclear hormone receptors (NRs) regulate the transcription of the target genes in response to binding with their ligands, which include metabolic and nutritional substrates. Among the various NRs, peroxisome proliferator-activated receptor γ promotes the transcription of adiponectin and antioxidative enzymes, whereas mineralocorticoid receptor mediates the effects of aldosterone and glucocorticoid to induce oxidative stress in adipocytes. It is hypothesized that both play crucial roles in the pathophysiology of obesity-associated insulin resistance and cardiovascular diseases. Thus, reduced adiponectin and increased oxidative stress play pathological roles in obesity-associated insulin resistance to increase

the cardiovascular disease risk, and various NRs may be involved in this pathogenesis.

Keywords: adipocytes; adiponectin; nuclear hormone receptors; obesity; oxidative stress.

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Introduction

Over the past few decades, obesity has been a growing threat to the health of people in an increasing number of countries [1]. Obesity, especially visceral fat obesity, causes insulin resistance and leads to the development of type 2 diabetes mellitus (T2DM), which is a strong risk factor for cardiovascular disease and cancers that are associated with a high mortality rate [2–4]. Furthermore, visceral fat obesity leads to the risk-clustering status known as metabolic syndrome, which is characterized by high plasma triglycerides (TG), low plasma high-density lipoprotein (HDL) cholesterol, high fasting plasma glucose, and high blood pressure, which is also a risk factor for cardiovascular events [5, 6]. A better understanding of the molecular basis of obesity will lead to the development of effective prevention strategies for obesity-associated cardiovascular diseases.

A series of studies have revealed that adipocytes generate and secrete a variety of endocrine factors known as adipokines/adipocytokines and that obesity-associated changes in adipocytokines contribute to the development of cardiovascular diseases [7]. Adiponectin, one of the most well-characterized adipocytokines, is produced exclusively by adipocytes and exerts insulin-sensitizing and anti-atherogenic effects [8–10]. Obese subjects have lower levels of circulating adiponectin [11, 12], which is recognized as a molecular factor contributing to obesity-induced insulin resistance and atherosclerosis.

Another important contributing factor for obesity-associated insulin resistance may involve low-grade chronic inflammation in adipose tissue [13, 14]. This inflammatory process includes an increase in pro-inflammatory

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adipocytokines [15–17] and an increase in oxidative stress [18]. In obese humans and rodents, the levels of oxidative stress-associated markers have been found to be elevated in plasma and urine [18]. In obese mice, oxidative stress was especially increased in adipose tissue [18]. This oxidative stress may remotely affect the oxidative stress levels in β cells [19, 20], vascular endothelium [21, 22], and the brain [23, 24], leading to the development of diabetes, hypertension, and atherosclerosis.

Nuclear hormone receptors (NRs) regulate the transcription of target genes in response to binding to their specific ligands, such as steroid hormones, fatty acids, oxysterol, and bile acids. NRs are expressed in tissues involved in lipid, carbohydrate, and energy homeostasis, translating hormonal, metabolic, and nutritional signals into alterations in gene expression [25]. In particular, peroxisome proliferator-activated receptor (PPAR) γ is an essential NR in adipocytes, playing an important role in the differentiation of mature adipocytes, and can promote the transcription of adiponectin and antioxidative enzymes [26–31]. Recently, mineralocorticoid receptor (MR) has been demonstrated to mediate the effects of aldosterone and glucocorticoid to induce oxidative stress in adipocytes [32–34]. Thus, many studies have shown that NRs play various roles in the pathophysiology of obesity-associated insulin resistance and cardiovascular diseases.

In this review, we describe the roles of reduced adiponectin and increased oxidative stress in obesity-associated insulin resistance as well as cardiovascular risk and the contribution of various NRs to the pathophysiology of obesity.

The roles of oxidative stress in obesity

Obesity-associated increase in oxidative stress in adipose tissue

The Framingham study revealed that urinary levels of 8-epi-prostaglandin F₂ α (8-epi-PGF₂ α), a systemic oxidative stress marker, were significantly associated with body mass index [35]. We have shown that urinary 8-epi-PGF₂ α levels are associated more closely with the visceral fat area than with the subcutaneous fat area measured by abdominal computed tomography [36]. In obese mice, the oxidative stress levels in plasma were elevated in comparison to those in control mice [18]. Moreover, lipid peroxide levels and hydrogen peroxide generation were elevated in adipose tissue, but not in the liver, skeletal muscle, or

aorta [18]. These data suggest that the adipose tissue in obese individuals may represent a major source of reactive oxygen species (ROS). The question is why oxidative stress increases in adipose tissue with obesity. Several possible explanations have been proposed.

Increased expression of nicotinamide adenine dinucleotide phosphate oxidase subunits

In adipose tissue, increased expression of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a plasma membrane enzyme that converts molecular oxygen to superoxide radicals, may be associated with increased oxidative stress levels. In obese mice, messenger ribonucleic acid (mRNA) expression of the NADPH oxidase subunits was increased in adipose tissue but not in the liver or muscles [18]. Moreover, treatment of obese mice with the NADPH oxidase inhibitor apocynin improved hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and hepatic steatosis [18]. These results suggest that ROS generation via NADPH oxidase could play an important role in the pathogenesis of obesity-associated metabolic disorder.

Decreased expression or activity of antioxidative enzymes

Adipose tissue expresses relatively high levels of antioxidant defensive enzymes. However, the expression and activity of antioxidant enzymes such as catalase, superoxide dismutase (SOD) 1, and glutathione peroxidase (GPx) were reduced in the adipose tissues of obese individuals [18, 28, 29, 37]. ROS dose-dependently suppress the expression of PPAR γ [18], an important transcriptional factor that induces the expression of catalase [28]. Interestingly, these changes in antioxidant levels were observed in adipose tissue but not in the liver or skeletal muscle. In addition to increased NADPH oxidase levels, decreased antioxidant levels may contribute to increased oxidative stress in the adipose tissue [18].

Involvement of adipose tissue macrophages

Macrophage infiltration into adipose tissue has been considered an important factor in the pathogenesis of insulin resistance in obese individuals [13, 14]. Macrophages are known to produce ROS; thus, adipose tissue macrophages could be involved in increased ROS generation. ROS have been shown to increase monocyte chemoattractant protein 1 (MCP-1) expression in adipocytes [18]. Furthermore, the by-products of ROS-associated lipid peroxidation

are potent chemoattractants [38]. ROS also augment the mRNA expression of NADPH oxidase subunits in adipocytes [18]; increased ROS generation could thus lead to increased macrophage infiltration and inflammatory changes. Therefore, in obesity, oxidative stress may contribute to the establishment of a vicious cycle that promotes increased inflammation in adipose tissues.

Overnutrition and ROS generation in mitochondria

Glucose is oxidized during the tricarboxylic acid cycle, which generates electron donors such as nicotinamide adenine dinucleotide dehydrogenase (NADH) and flavin adenine dinucleotide (FADH₂). Excess glucose leads to the overproduction of electron donors in the mitochondrial electron transport chain, resulting in the generation of superoxide radicals [39]. Similarly, excess free fatty acids (FFAs) lead to increased FFA oxidation by mitochondria, which in turn generate excess NADH and FADH₂, leading to the mitochondrial overproduction of ROS [39]. Furthermore, ROS generation is augmented in FFA-loaded adipocytes but can be blocked by treatment with an NADPH oxidase inhibitor, indicating the involvement of NADPH oxidase in ROS generation by fatty acids [18]. FFAs, especially palmitate, can stimulate diacylglycerol synthesis and activate protein kinase C (PKC), which leads to the activation of NADPH oxidase [40]. Thus, excess glucose and FFAs cause oxidative stress in mitochondria and the plasma membrane.

Taken together, various mechanisms, including increased NADPH oxidase expression and decreased antioxidant activities, may be involved in the increased ROS generation by adipose tissue in obesity.

Increased oxidative stress in obesity and insulin resistance

Many studies have reported an association between ROS and insulin resistance [37, 41–45]. In 3T3-L1 adipocytes, insulin resistance can be induced by treatment with either tumor necrosis factor (TNF- α) or glucocorticoid, via increased ROS generation, whereas treatment with an antioxidative agent, either SOD or catalase, can improve insulin resistance [41]. Oxidative stress has also been reported to induce insulin resistance in myocytes [45]. This ROS-induced insulin resistance can be attributed to the activation of stress signals such as c-Jun N-terminal kinase, p38 mitogen-activated protein kinase, nuclear factor κ B (NF- κ B), and certain isoforms of PKC [39, 41–43].

Meanwhile, hydrogen peroxide is produced transiently in response to insulin in a NADPH oxidase-mediated manner and acts as a second messenger to augment insulin signals in adipocytes [44]. These data indicate that, in adipocytes, transient increases in cellular ROS may play an important role in insulin signaling, but excessive and prolonged exposure to ROS suppresses insulin action. Glutathione (GSH) has been shown to overaccumulate in hypertrophied adipose tissues [37]. Although GSH is an antioxidant, excess GSH suppresses insulin action in adipocytes [37]. Meanwhile, insulin suppresses GPX activity, which leads to the accumulation of GSH in adipocytes [37], indicating a complex interaction between insulin and ROS in adipocytes. In β -cells and isolated islets, oxidative stress suppresses insulin production [19, 46]. This impaired insulin production can be improved with antioxidant treatment in obese mice [20]. Increased oxidative stress impairs insulin production as well as insulin action.

Increased oxidative stress in obesity and cardiovascular disease

Oxidative stress is strongly involved in the development of atherosclerosis [47]. Excess ROS attenuates nitric oxide bioavailability, and superoxide easily reacts with nitric oxide, leading to the generation of harmful peroxynitrite and, subsequently, to endothelial dysfunction [22]. Increased ROS facilitates the oxidation of low-density lipoprotein (LDL) in atherosclerotic lesions [48], thus facilitating immune reactions in endothelial cells, including the increased expression of adhesion molecules, which results in macrophage migration, and the formation of lipid-laden macrophages [47]. These processes aggravate vascular endothelial damage.

Several mechanisms that increase oxidative stress locally in the vascular wall have been postulated as atherosclerosis pathogenesis. Increased NADPH oxidase expression has been observed in pre-atherosclerotic vascular endothelium [49, 50], whereas angiotensin II acts through the angiotensin type I receptor to trigger a powerful stimulus for ROS generation from NADPH oxidase [21, 51].

Several molecules may be involved in the modulation of hyperglycemia-induced oxidative stress, including those in the polyol pathway, advanced glycation end products (AGEs), and PKC [52–55]. The polyol pathway is facilitated by hyperglycemic states. Aldose reductase, a polyol pathway enzyme, utilizes and depletes NADPH to convert excess glucose to sorbitol. In particular, AGE-receptor interactions activate NADPH oxidase, leading to ROS generation [56]. Mitochondrial ROS (described in a previous

section) are also involved in cellular AGE accumulation, activation of the polyol pathway, and PKC [54]. These oxidative stresses are aggravated in obesity and diabetes.

The prolonged presence of increased TG-rich lipoproteins in the circulation induces oxidative stress in the endothelium [57, 58]. Our recent clinical study suggested that in high-risk DM patients treated with statins, the circulating levels of malondialdehyde-modified LDL (MDA-LDL), a surrogate marker of oxidized LDL, were significantly correlated with the TG and HDL cholesterol levels [59]. Adiponectin levels were also significantly correlated with MDA-LDL levels, although not independently of TG and HDL cholesterol [59]. The serum MDA-LDL level was significantly associated with serum remnant lipoprotein cholesterol levels [59]. Activation of lectin-like oxidized LDL receptor 1 by remnant lipoprotein particles induced NADPH oxidase-dependent production of superoxide in endothelial cells [60], which may explain the significant association between LDL oxidation and remnant lipoproteins rich in TG. Moreover, HDL protects against the oxidation of LDL [61]. Collectively, the management of dyslipidemic metabolic syndrome components is important for reducing the oxidation of LDL, and ultimately, to the development of atherosclerosis (Figure 1).

Roles of adiponectin in obesity-associated insulin resistance and cardiovascular risk

Clinical implications of adiponectin in obesity-associated diseases

Circulating levels of adiponectin are low in patients with visceral fat obesity [11] or T2DM [12], and the levels are correlated with the indices of insulin sensitivity [62, 63]. People with high levels of circulating adiponectin are less likely than those with low concentrations to develop T2DM [64]. Circulating adiponectin levels are also decreased with hypertension in humans, irrespective of insulin resistance [65]. Furthermore, adiponectin concentrations correlate positively with HDL cholesterol concentrations and negatively with TG concentrations [66]. Patients with missense mutations in the adiponectin gene present with low adiponectin concentrations and have been reported to exhibit T2DM and metabolic syndrome phenotypes [67]. Thus, low circulating adiponectin levels are associated with various coronary risk factors. A case-control study demonstrated that

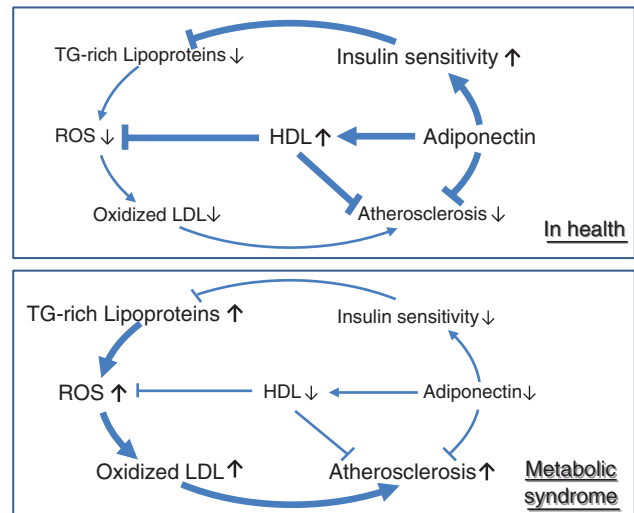


Figure 1 Schematic diagram of the effects of adiponectin and oxidative stress on circulating lipoproteins and atherosclerosis under healthy conditions and in metabolic syndrome.

In metabolic syndrome, the reduction of adiponectin leads to the increase of TG-rich remnant lipoproteins via decreased insulin sensitivity, which contributes to generation of ROS, resulting in the oxidation of LDL that accelerates the development of atherosclerosis. Moreover, the anti-atherosclerosis force is ameliorated directly by the reduction of adiponectin and indirectly through the decrease of HDL that contributes to reverse cholesterol transport and suppresses the oxidation of LDL.

low adiponectin levels are associated with a high risk of coronary artery disease [68], whereas a clinical prospective study demonstrated that men with high circulating adiponectin levels had a significantly lower prevalence of myocardial infarction than those with low adiponectin levels [69]. Recent clinical studies have demonstrated that low levels of circulating adiponectin are significantly associated with lipid-rich plaques in coronary arteries, as assessed by intravascular ultrasound [70]. Low adiponectin levels were significantly associated with multivessel coronary atherosclerosis assessed on computed tomography angiography independently of conventional risk factors in patients with suspected coronary artery disease and were predictive of multivessel coronary atherosclerosis in combination with age, sex, hypertension, and diabetes [71]. Taken together with the basic researches described in detail in the following sections, these clinical studies indicate that circulating adiponectin protein should directly protect coronary artery walls from pro-atherogenic stresses induced by conventional risk factors as well as enhance insulin sensitivity, and hence, the vascular walls with reduced adiponectin protein should be susceptible to pro-atherogenic stresses, facilitating the development of coronary atherosclerosis.

Insulin-sensitizing effects of adiponectin

The insulin-sensitizing or anti-diabetes effects of adiponectin have been demonstrated in vivo in animal studies. Adiponectin-deficient mice showed marked elevations in plasma glucose and insulin levels, as well as insulin resistance, relative to wild-type mice, when fed a high-fat and high-sucrose diet, although they did not present this phenotype on a normal diet [9]. Adiponectin supplementation via transfection with an adiponectin-generating adenovirus reduced the development of insulin resistance in adiponectin-deficient mice that consumed a high-fat and high-sucrose diet [9].

A study by Kadowaki and his colleagues has elucidated the precise molecular mechanism involved in the adiponectin-mediated modulation of insulin sensitivity. Adiponectin exerts insulin-sensitizing effects via adenosine monophosphate-activated protein kinase (AMPK) activation and facilitates fatty acid oxidation via PPAR α activation [72]. These effects are mediated by the membrane receptor proteins AdipoR1 and AdipoR2, which specifically bind to adiponectin [73]. Analysis of mice deficient in both AdipoR1 and AdipoR2 revealed that these proteins play essential roles in mediating the effects of adiponectin with regard to insulin sensitization and the suppression of inflammation or oxidative stress [74].

Anti-inflammatory and anti-atherogenic effects of adiponectin

Anti-atherosclerotic effects have been demonstrated in vivo in animal studies of adiponectin-deficient mice. When compared with wild-type mice, adiponectin-deficient mice developed more severe intimal thickening, with more active smooth muscle cell proliferation after receiving an experimental vascular injury [10]. Treatment with adiponectin-producing adenovirus suppressed this intimal thickening [10]. Adiponectin overexpression attenuated plaque formation in apolipoprotein E-deficient mice [75, 76]. The various biological properties of adiponectin that suppress pro-inflammatory or pro-atherosclerotic processes have been elucidated. Adiponectin can suppress the expression of adhesion molecules, such as intracellular adhesion molecule 1, by inhibiting the TNF- α -mediated activation of NF- κ B in endothelial cells, leading to the suppression of monocyte adhesion, which is an initial step in atherosclerosis [77]. Adiponectin predominantly inhibits the proliferation of myelomonocytic lineage cells and suppresses mature macrophage functions, including phagocytic activity

and lipopolysaccharide-induced TNF- α production [78]. In macrophages, adiponectin can suppress foam cell transformation by inhibiting scavenger receptor class A expression [79]. Adiponectin overexpression significantly reduces the vascular wall expression of scavenger receptor class A, TNF- α , and intracellular adhesion molecule 1 in apolipoprotein E-deficient mice and suppresses atherosclerosis [75, 76]. It also suppresses growth factor-induced vascular smooth muscle cell proliferation by inhibiting mitogen-activated protein kinase [80]. Furthermore, adiponectin increases the expression of a tissue inhibitor of metalloproteinase in macrophages, which contributes to coronary artery plaque stabilization by inhibiting matrix metalloproteinases [81]. The adiponectin protein exists in the aortic endothelium under steady state conditions and may protect vasculature from the initiation of atherosclerosis [82]. Adiponectin increases HDL assembly by enhancing the ATP-binding cassette transporter A1 (ABCA1) pathway and apolipoprotein A-1 synthesis in the liver [83, 84], leading to an enhancement of reverse cholesterol transport. Collectively, these properties contribute to the anti-atherosclerotic and anti-inflammatory functions of adiponectin.

The oxidative stress and adiponectin antagonism

Adiponectin suppresses the harmful effects of oxidative stress

Besides its suppressive effects on atherosclerosis, adiponectin inhibits pressure overload-induced myocardial hypertrophy, decreases angiotensin II-induced cardiac fibrosis, and protects the heart from ischemia-reperfusion injury [85–87]. In a myocardial infarction/reperfusion model, adiponectin played a protective role against oxidative stress-induced myocardial damage. It is possible that adiponectin decreases oxidative/nitrative stress by inhibiting inducible nitric oxide synthase and suppressing the expression of gp91^{phox}, a NADPH oxidase subunit [88], in an AMPK-independent manner [89]. Similar effects of adiponectin have also been observed in the endothelium. Adiponectin can suppress oxidative/nitrative stress in the arteries of hyperlipidemic rats [90]. In addition, adiponectin exerts cardioprotective effects against the oxidative stress-induced remodeling processes in cardiomyocytes by activating AMPK and inhibiting extracellular signal-regulated kinases and NF- κ B [91]. Interestingly, this cardioprotective effect of

adiponectin was reduced in mice in which diabetes was induced through a high fat diet [92], which may be associated with reduced AdipoR1 and AdipoR2 expression in response to insufficient insulin activity [93].

Oxidative stress suppresses adiponectin production

In humans, serum adiponectin levels are inversely correlated with systemic oxidative stress [18, 36]. In adipose cells, ROS exposure suppressed adiponectin mRNA expression and secretion and increased the mRNA expression of pro-inflammatory adipocytokines such as interleukin (IL) 6 and MCP-1 [18]. The antioxidant *N*-acetylcysteine reversed the effects of ROS and restored gene expression to the basal level [18]. Furthermore, in an in vivo study, treatment of obese mice with apocynin, an NADPH oxidase inhibitor, led to increased adiponectin expression and decreased TNF- α expression, which were accompanied by the suppression of oxidative stress in the adipose tissue [18]. These data suggest that oxidative stress plays a role in reducing adiponectin levels, which in turn contributes to obesity-associated disease pathogenesis. Conversely, oxidative stress was enhanced in AdipoR1- and AdipoR2-deficient mice [74], which provides evidence that the adiponectin-AdipoR pathway contributes to the suppression of oxidative stress.

Roles of NRs in obesity-associated insulin resistance and cardiovascular risk

Peroxisome proliferator-activated receptors

PPAR γ is a master regulator that plays a key role in the control of adipocyte-specific gene expression in combination with CCAAT/enhancer binding protein α during adipose differentiation [26]. PPAR γ 2 is exclusively expressed by adipocytes and plays essential roles in regulating various important genes involved in adipose differentiation as well as in glucose and lipid metabolism in adipocytes. Thiazolidinediones (TZDs), synthetic PPAR γ ligands, can improve insulin resistance [94]. TZDs can increase circulating adiponectin levels by activating adiponectin gene transcription through a PPAR γ -responsive element in the gene promoter region [27]. Kubota et al. [95] demonstrated that TZDs exert insulin-sensitizing effects in *ob/ob* mice, mainly by activating AMPK and suppressing

gluconeogenesis in the liver. This effect is mediated partly by an adiponectin-dependent pathway.

PPAR γ plays an important role in the transcriptional activation of antioxidant enzymes such as SOD1, catalase, and GPX3 [28–31]. The expression of these antioxidant enzymes is decreased in the adipocytes of obese animals [18, 31, 37], whereas TZDs increase the expression, which may contribute to the suppression of oxidative stress [28, 29, 31]. TZDs have been shown to suppress TNF- α -induced oxidative stress [57]. Therefore, the insulin-sensitizing effects of TZDs might be explained partly by their ability to inhibit oxidative stress. Interestingly, PPAR γ -mediated regulation of catalase is functionally conserved between mice and humans, although the locations of the PPAR γ -responsive sites in the promoter regions are different [28, 29]. Clinically, a randomized controlled trial revealed that pioglitazone, a TZD, reduces the incidence of all-cause mortality, nonfatal myocardial infarction, and stroke in patients with type 2 diabetes, who have a high risk of macrovascular events [96]. PPAR γ could prove to be a therapeutic target for insulin resistance to reduce cardiovascular risk, especially in obese subjects.

Although other PPARs are not key regulators of adipogenesis, they can control lipid metabolism. Activation of PPAR α results in a reduction of plasma TG levels, through the induction of genes that decrease the availability of TG for hepatic very-low-density lipoprotein secretion, and the induction of genes that promote lipoprotein lipase-mediated lipolysis of TG-rich plasma lipoproteins [97]. Fibrates, synthetic ligands of PPAR α , can increase the production of adiponectin via PPAR α in adipocytes [98]. Several clinical trials have suggested that fibrates may be effective for the prevention of cardiovascular events in patients with high TG and low HDL-C levels [99, 100]. PPAR δ induces the expression of genes required for fatty acid oxidation and energy dissipation in skeletal muscle and contributes to the development of oxidative muscle fiber [101, 102]. Activation or overexpression of PPAR δ in mice results in resistance to weight gain and improved insulin sensitivity in high fat diet-induced obesity, as well as genetically predisposed obesity, via enhanced oxidation [103].

Mineralocorticoid receptor

Recent studies have resulted in a better understanding of MR physiology in the heart, vasculature, brain, and adipose tissues [104]. Activation of MR by aldosterone promotes ROS generation through NADPH oxidase in the heart and vasculature [105]. Recent studies have revealed that MR was also involved in oxidative stress in adipose tissue

[32–34]. Adipose expression of MR increases in obese mice [33]. Treatment of obese mice with eplerenone, an inhibitory agent of MR, can improve insulin resistance through the suppression of macrophage infiltration, a decrease in inflammatory adipocytokines, and an increase in serum adiponectin levels [32]. Similarly, in 3T3-L1 adipocytes, treatment with aldosterone suppresses the expression of adiponectin, which is blocked by eplerenone [33]. Moreover, aldosterone increases oxidative stress in 3T3-L1 adipocytes, which is blocked by treatment with eplerenone or small interfering RNA of MR, indicating that the effect of aldosterone is mediated by MR [33].

MR can bind not only to aldosterone but also to glucocorticoid, with 10-fold higher affinity than the glucocorticoid receptor (GR) [106]. Glucocorticoids are a potent regulator of adipose differentiation, which is mediated by MR [107]. A selective MR blockade can inhibit adipose differentiation and TG accumulation in 3T3-L1 and 3T3-F442A cells [108]. 11 β -Hydroxysteroid dehydrogenase type 1 (11 β -HSD1), an enzyme that converts cortisone to active cortisol, is expressed in adipose tissue [109]. 11 β -HSD1 mRNA in adipose tissue is expressed more highly in obese subjects, suggesting that active cortisol has a role in the pathophysiology of obesity [110, 111]. Fat-specific overexpression of 11 β -HSD1 shows a phenotype presenting abdominal obesity, hypertension, and insulin resistance [112]. In 3T3-L1 adipocytes, treatment with glucocorticoid increases the expression of NADPH oxidase subunits, leading to an increase in oxidative stress [34], and decreases the expression of adiponectin and catalase (Figure 2), which is blocked by treatment with eplerenone, suggesting that these effects of glucocorticoid are mediated by MR in adipocytes [34]. The expression and activity of 11 β -HSD1 in adipocytes is negatively regulated by PPAR γ [113]. Therefore, the reduction of PPAR γ leads to an increase in 11 β -HSD1 activity, resulting in greater generation of cortisol, leading to increased oxidative stress through MR, which in turn causes a further reduction in PPAR γ (Figure 2). This vicious cycle mediated by inappropriate MR activation (by both aldosterone and glucocorticoids) should be associated with the development of insulin resistance and atherosclerosis [114] (Figure 2), which can be blocked by treatment with TZDs or eplerenone.

Meanwhile, selective GR stimulation inhibits the expression of pro-inflammatory adipocytokines [115]. A recent research have revealed that cardiomyocyte-specific GR-deficient mice die prematurely from spontaneous cardiovascular disease or display a marked reduction in left ventricular systolic function by 3 months of age [116]. Thus, glucocorticoids via activating GR play a crucial role in protecting target tissues from stresses, whereas they induce oxidative stress via activating MR.

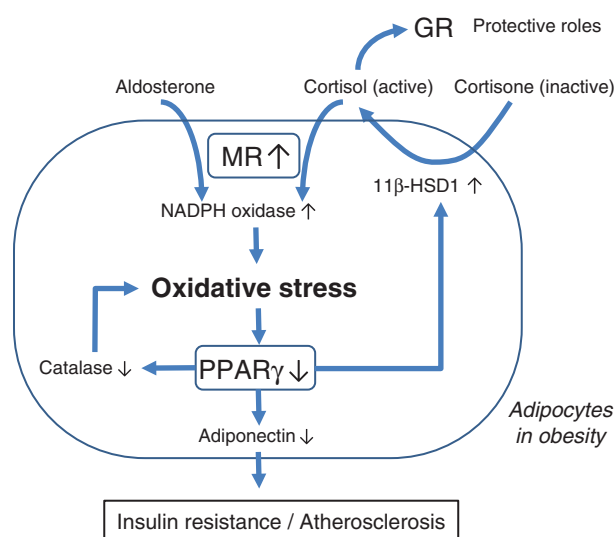


Figure 2 Working model illustrating the contribution of nuclear receptors to increased oxidative stress and decreased adiponectin expression in adipocytes in obesity.

Inappropriate MR activation by both aldosterone and cortisol leads to increased oxidative stress via the activation of NADPH oxidase, which ameliorates PPAR γ , which plays an essential role in the expression of adiponectin. The reduction of adiponectin is causally associated with the development of insulin resistance and atherosclerosis. Moreover, the inactivation of PPAR γ causes the reduction of catalase, leading to further increase of oxidative stress and increase of 11 β -HSD1, which facilitates the conversion of inactive cortisone to active cortisol, which further activates MR activity.

Liver X receptors

There are two liver X receptors (LXRs), termed LXR α and LXR β . LXR α is expressed in liver, intestine, macrophages, and adipose tissue, whereas LXR β is ubiquitously expressed [117]. LXR regulates the expression of the ABCA1 [118, 119], which is one of the important transporters for reverse cholesterol transport, the process of cholesterol delivery from the periphery to the liver. A synthetic LXR agonist has been demonstrated to inhibit the development of atherosclerosis in mice [120]. Meanwhile, LXR stimulates lipogenesis through the induction of sterol-regulatory element-binding protein 1c (SREBP1c), a transcriptional factor activating various genes involved in lipogenesis [121]. In addition, LXR activation leads to hypertriglyceridemia via the expression of angiopoietin-like protein 3, suppressing lipoprotein lipase activity [122]. Thus, LXR agonists have a beneficial effect of inhibiting atherosclerosis, but they also have a harmful effect of promoting hepatic steatosis and hypertriglyceridemia.

Both LXRs are highly expressed in white and brown adipose tissues. Although LXRs do not contribute to

adipocyte differentiation, they regulate the genes involved in adipocyte growth and glucose homeostasis [123, 124]. LXR activation promotes the expression of glucose transporter 4 (GLUT4) and increases glucose uptake in adipose tissue [125, 126]. Meanwhile, LXR increases fatty acid β -oxidation and decreases glucose oxidation in white adipose tissue [127]. LXR-deficient mice are resistant to diet-induced obesity, which may be mediated by increased energy expenditure in brown adipose tissue [128, 129]. Collectively, these data suggest that LXRs play some role in governing glucose and lipid metabolism in adipose tissue.

Other nuclear hormone receptors

Farnesoid X receptor (FXR), liver receptor homologue 1 (LRH-1), and a small heterodimer partner (SHP) are NRs that have been shown to regulate various genes involved in bile acid metabolism [130–132]. In mice fed a high-fat diet, FXR deletion had a protective effect, reducing weight gain, hyperglycemia, hyperinsulinemia, and glucose intolerance, despite higher plasma TG levels [133]. Meanwhile, FXR activation reduced atherosclerotic lesion formation in LDL receptor null or apolipoprotein E null mice [134]. LRH-1 augments PPAR γ -induced transactivation of the *adiponectin* gene [27]. Treatment with an LRH-1 ligand leads to decreased hepatic TGs and serum glucose [135]. Mutations of the *SHP* gene are associated with a mildly obese phenotype in Japanese subjects [136]. Meanwhile, SHP knockout mice are resistant to diet-induced obesity [137, 138]. Although the precise mechanism has not yet been fully clarified, SHP has been reported to modulate the activity of PPAR γ [139] and PPAR α [137]. Other NRs such as chicken ovalbumin upstream promoter transcription factor II [140, 141], RAR-related receptor α (ROR α) [142], estrogen-related receptor α (ERR α) [143], ERR γ [144], and REV-ERB α [145] have been shown to be involved in adipogenesis. In the future, the identification of new ligands for NRs may facilitate the development of new therapeutic approaches for the treatment of patients with obesity and insulin resistance to reduce cardiovascular risk, although further studies are required.

Expert opinion

Measuring circulating adiponectin levels and oxidative stress levels is beneficial because they give an indication of obesity-associated cardiovascular risk and are

predictive of the occurrence of severe cardiovascular disease, in combination with conventional risk factors. TZDs and eplerenone increase adiponectin levels and decrease oxidative stress levels via the activation of PPAR γ and suppression of MR, respectively. Other NRs in adipocytes may be good drug targets for obesity-associated insulin resistance and cardiovascular diseases.

Outlook

The identification of new ligands for NRs will facilitate the development of new therapeutic approaches for the treatment of patients with obesity and insulin resistance to reduce cardiovascular risk.

Highlights

- Adiponectin is an adipocyte-derived factor that has insulin-sensitizing and anti-atherogenic functions. In obese subjects, plasma adiponectin levels are reduced, which facilitates the development of diabetes and atherosclerosis.
- In obese subjects, oxidative stress levels are elevated in adipose tissue, which affects the remote organs, contributing to the development of obesity-associated diseases, such as diabetes, hypertension, and atherosclerosis.
- Adiponectin and oxidative stress are co-associated. Oxidative stress suppresses the production of adiponectin in adipocytes. Adiponectin suppresses oxidative stress-induced damage in the heart and the vascular wall.
- PPAR γ is an essential NR for adipocyte differentiation and regulates the transcription of various genes involved in glucose and lipid metabolism in adipocytes. Oxidative stress suppresses the expression of PPAR γ , leading to amelioration of adipocyte function.
- TZDs, synthetic ligands of PPAR γ , can increase the expression of adiponectin and antioxidative enzymes, such as catalase, SOD1, and GPX3.
- MR is an NR expressed in adipocytes that mediates the effect of aldosterone and glucocorticoid to increase oxidative stress.
- Treatment of obese mice with eplerenone, an MR antagonist, can decrease oxidative stress and increase adiponectin expression in adipose tissue.
- There are a number of NRs in adipocytes that may be involved in obesity-associated diseases. Activation

or repression of these NRs will be targets for the development of new therapeutic approaches to obesity-associated insulin resistance and atherosclerosis.

Conflict of interest statement: The authors declare no conflict of interest.

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