Adiposity and Cardiovascular Disorders
Disturbance of the Regulatory System Consisting of Humoral and Neuronal Signals

Hideki Katagiri, Tetsuya Yamada, Yoshitomo Oka

Abstract—Obesity, a major healthcare issue, is associated with significant cardiovascular morbidities, including hypertension and atherosclerosis. Numerous intensive studies conducted this decade have revealed that adipose tissue is a major endocrine organ that secretes a variety of bioactive substances, termed adipocytokines. Adipocytokine secretion profiles are altered as obesity develops, which may increase the risk of obesity-related cardiovascular disorders. For instance, leptin is upregulated in obese subjects and plays important roles in the pathophysiology of obesity-related atherogenesis through multiple mechanisms, such as its proliferative, proinflammatory, prothrombotic, and prooxidant actions. In contrast, adiponectin, which is downregulated in obese subjects, has protective effects against cardiovascular disorders at various atherogenic stages. In addition to these factors secreted by adipose tissue, neuronal circuits involving autonomic nerves are now being recognized as an important metabolic regulatory system and have thus attracted considerable attentions. Alterations in fat accumulation in intraabdominal organs, such as visceral adipose tissue and the liver, send afferent neuronal signals to the brain, leading to modulation of sympathetic tonus and thereby affecting the vasculature. Moreover, these humoral and neuronal signaling pathways communicate with each other, resulting in cooperative metabolic regulation among tissues/organs throughout the body. Further elucidation of these regulatory systems is anticipated to lead to new approaches to devising therapeutic strategies for the metabolic syndrome. (Circ Res. 2007;101:27-39.)

Key Words: adipocytokines ■ autonomic nervous system ■ metabolic syndrome ■ atherosclerosis ■ hypertension

Excess food intake and physical inactivity underlie the growing worldwide epidemic of obesity, not only in the industrialized nations but also in developing countries. A variety of common disorders, eg, hyperglycemia, hyperlipidemia, and hypertension, are common in obese individuals. Such disorders are not clustered coincidently, and intraabdominal visceral adiposity has been suggested to play a fundamental role in the simultaneous development of these
disorders, collectively termed the metabolic syndrome. In addition, one of the major challenges of this syndrome is the high prevalence of cardiovascular diseases arising from atherosclerosis.

Visceral fat accumulation may be directly associated with the development of cardiovascular disease. Epidemiological studies have suggested that visceral adiposity, as evaluated by the waist-to-hip ratio or computed tomography scanning, is related to coronary artery disease independently of body mass index. Recent intensive studies have revealed that humoral factors secreted by adipose tissue contribute to the development of the metabolic syndrome and vascular diseases.

Adipose tissues were long regarded as nothing more than passive fuel storage sites. However, recent studies have revealed that adipocytes, as well as other cells within fat tissues, release numerous biologically active substances, termed adipocytokines, leading to the concept of adipose tissue as a versatile endocrine gland. Obesity, especially visceral fat accumulation, alters adipocytokine secretion profiles, and obesity-related disorders are now recognized as a state of adipose tissue dysfunction. Cardiovascular morbidity in obese individuals might be explained by adipocytokine secretion profile alterations, which result mainly from enlargement of adipocytes and proinflammatory changes in adipose tissue. In addition, recent studies, including ours, have revealed that adiposity in intraabdominal tissues, such as the liver and visceral adipose tissues, directly influences the autonomic nervous system, and thereby modulates sympathetic tonus.

The present review focuses on the effects of different adipocytokines on vascular functions. In addition, we further discuss intertissue communication of metabolic information via the autonomic nervous system in obesity-related disorders.

Humoral Factors Involved in Metabolic Regulation

Humoral Factors Derived From Adipose Tissue

Adipocytes produce and secrete a number of bioactive substances, including polypeptides and nonprotein factors that are known to exert a wide variety of effects on glucose and lipid metabolism, energy homeostasis, and cardiovascular function, among others. These substances, collectively called adipocytokines, include leptin, adiponectin, resistin, angiotensinogen, tumor necrosis factor (TNF)-α, plasminogen activator inhibitor (PAI)-1, visfatin, retinol-binding protein (RBP-4), fatty acids, sex steroids, and various growth factors. Insulin resistance is an important factor in the development of coronary heart disease, as evidenced by studies in both animal models and humans. Adipocytokines act synergistically or competitively with insulin. Therefore, these factors directly or indirectly affect vascular function and have the potential to provide useful insights into the pathogenesis of vascular disease.

Here we present the current understanding of the complex roles of adipocyte-derived hormones, in particular leptin and adiponectin, in endothelial cell function and the pathogenesis of atherosclerotic vascular disease (Figure 1).

**Leptin**

Leptin was identified by positional cloning in the *ob*/*ob* mouse model as a key molecule in the regulation of body weight and energy balance. Leptin is a 167-aa secreted protein encoded by the *ob* gene. Leptin is mainly produced and secreted by adipocytes. Leptin acts on the hypothalamus, altering energy intake by decreasing appetite and increasing energy expenditure via sympathetic stimulation of several tissues. Adipocyte leptin expression is transcriptionally regulated, as determined mainly by the status of the energy stores in white adipose tissue and the size of adipocyte sizes. Thus, leptin plays versatile role in maintaining energy homeostasis by communicating information regarding the energy-storage status of adipose tissue to the brain. For instance, with increasing energy storage, the energy balance is negatively regulated by decreased food intake and increased energy expenditure.

Leptin receptors were first isolated from the mouse choroid plexus by expression cloning but are also present in several other tissues, including the hypothalamus. Positional cloning of the *db* locus encoding leptin receptors revealed at least 6 alternatively spliced forms, leptin receptor (Ob-R)a through Ob-Rf. Among these receptor isoforms, Ob-Rb, also termed the long isoform, is highly expressed in the hypothalamus and mediates the anorectic effect of leptin. Ob-Rb contains the longest intracellular domain, which, on ligand binding, activates protein tyrosine kinases of the Janus kinase family–signal transducers and activators of transcription (JAK-STAT) pathway. Other short isoforms, including Ob-Ra, Ob-Rc, Ob-Rd, and Ob-RI, do not activate the JAK-STAT pathway. Subsequent research demonstrated that the effects of leptin are not restricted to the energy balance. The long form Ob-Rb is expressed throughout the body and has also been detected in endothelial cells. Leptin is a pleiotropic molecule with a wide range of biological actions, including...
reproductive functions, regulating the hypothalamic–pituitary–adrenal axis, glucose and insulin metabolism, lipolysis, immune responses, hematopoiesis, and angiogenesis.

**Leptin and the Vasculature**

Several reports have suggested either a vasodilatory or vasoconstrictive action of leptin, which would be direct on the vascular wall. First, the vasodilatory action of leptin is supported by experimental results showing that endothelial-dependent vasorelaxant responses to acetylcholine are markedly impaired in microvessels from leptin-deficient ob/ob mice and that leptin restoration reverses the endothelial dysfunction observed in these mice.\(^{12}\) Leptin has been shown to promote nitric oxide (NO) release from the vascular endothelium, thereby potentially decreasing blood pressure.\(^{13,14}\) However, in these reports, decreased blood pressure in response to leptin treatment was observed in only sympathectomized rats. In addition, systemic leptin administration does not attenuate the renal and hindlimb vasoconstriction resulting from sympathetic nerve stimulation.\(^{15}\) These findings suggest that the NO-dependent vasodilatory effects of leptin are insufficient to counter sympathetically mediated vasoconstriction. Furthermore, in vitro treatment of human umbilical vein endothelial cells (HUVECs) with leptin induced endothelin-1, known to be a potent vasoconstrictor.\(^{16}\) Thus, although high concentrations of leptin may exert vasodilatory effects, the exact vasodilatory actions of leptin remain uncertain.

On the other hand, considerable evidence obtained from animal studies indicates that leptin may modulate arterial pressure through sympathetic mechanisms. In rats, acute intravenous\(^8\) and intracerebroventricular\(^{17}\) administration of leptin has been shown to increase sympathetic nerve signals to brown adipose tissue, kidneys, adrenal glands, and hindlimbs. Chronic intracarotid\(^{18}\) and intracerebroventricular\(^{19}\) administration of leptin also raises blood pressure in rats. Transgenic mice overexpressing leptin in the liver develop hypertension, which is reversed by \(\alpha_1\)-adrenergic, \(\beta\)-adrenergic, or ganglionic blockers.\(^{20}\) Furthermore, despite severe obesity, leptin-deficient ob/ob mice have lower blood pressure than lean controls,\(^{21}\) whereas administering exogenous leptin to ob/ob mice raises blood pressure to the levels of lean controls.\(^{20}\) Thus, leptin has unequivocal sympathoexcitatory actions in rodents. In humans as well, there is a positive relationship between mean blood pressure and serum leptin levels in lean subjects with essential hypertension.\(^{22}\) In human subjects with widely differing degrees of adiposity, renal norepinephrine spillover correlates with plasma leptin concentrations after adjusting for adiposity,\(^{23}\) whereas giving leptin to lean subjects for 6 days had no impact on norepinephrine, dopamine, or epinephrine levels in 24-hour urine samples.\(^{24}\) Further studies are needed to obtain conclusive evidence of the sympathoexcitatory effects of leptin on blood pressure in humans.

**Leptin Resistance and Hypertension**

Obese subjects remain hyperphagic despite their high circulating leptin levels, indicating hypothalamic insensitivity to leptin, a state termed leptin resistance. This was confirmed by clinical trials in which leptin given to obese patients produced only modest effects on body weight.\(^{25}\) However, despite severe leptin resistance, the sympathoexcitatory effect of leptin, as evaluated by neurography of renal sympathetic nerves, is reportedly preserved after either systemic or central neural administration of leptin.\(^{26}\)

In mice with dietary obesity, food intake suppression and body weight gain induced by intraperitoneal or intracerebroventricular leptin were significantly attenuated, whereas the renal sympathoexcitatory response to leptin was preserved, leading to substantially elevated arterial pressure. The leptin-dependent increases in arterial pressure were of similar magnitude in mice fed either a high-fat diet or normal chow.\(^{27}\) These findings led to the notion of selective leptin resistance in which, despite resistance to the anorexigenic effect of leptin, sympathetic nerves are normally activated in response to leptin. In human subjects, there is a strong correlation between leptin plasma concentrations and renal sympathetic activation, as shown in men with widely differing degrees of adiposity.\(^{23}\) Thus, selective leptin resistance and the resultant sympathetic activation in response to hyperleptinemia may contribute to development of hypertension in patients affected with the metabolic syndrome.

**Leptin and Atherosclerosis**

A number of observations indicate a correlation between serum leptin and the pathogenesis of atherosclerotic vascular disease. Human plasma leptin concentrations are independently associated with intima–media thickness in the common carotid artery, an early marker of atherosclerosis.\(^{28}\) Elevated leptin concentrations in healthy adolescents are associated with decreased arterial distensibility within a broad range of body mass indices.\(^{29}\) In a major prospective cohort investigation, the West of Scotland Coronary Prevention Study, serum leptin levels were moderately associated with coronary heart disease, independently of other risk factors.\(^{30}\) In addition, leptin levels independently predict future cardiovascular events in subjects with established coronary atherosclerosis.\(^{31}\)

In mouse studies as well, there is growing evidence of the contribution of leptin to the development of atherosclerosis. Wild-type mice on an atherogenic diet show leptin elevation and greater neointimal wall thickening after carotid artery injury with high leptin receptor expression in the lesion. In contrast, ob/ob mice are markedly resistant to diet-induced formation of atherosclerosis, despite the presence of atherosclerosis risk factors such as diabetes, obesity, and hyperlipidemia. Exogenously administered leptin induces wall thickening in ob/ob mice but not in db/db mice.\(^{32}\) Thus, there might be a direct link between hyperleptinemia and an increased risk for cardiovascular disease development in obese subjects. Possible mechanisms underlying the atherogenic actions of leptin will be discussed below.

**Proliferative Actions of Leptin**

The vascular proliferative actions of leptin are exerted mainly via activations of mitogenic factors. For instance, leptin in culture media dose-dependently increases both the migration and the proliferation of rat vascular smooth muscle cells through activation of phosphatidylinositol-3-kinase and mitogen-activated protein kinases.\(^{33}\) Neointimal formation
after endovascular arterial injury is markedly attenuated in db/db mice, suggesting a role for leptin in endothelial intimal layer regeneration after vascular injury. Thus, leptin may contribute to vascular remodeling and perhaps arterial restenosis after angioplasty.

**Proinflammatory Actions of Leptin**

Stimulation of low-grade vascular inflammation is another mechanism whereby leptin may promote both endothelial dysfunction and atherogenesis. In ob/ob and db/db mice, phagocytosis and the expressions of proinflammatory cytokines, such as TNF-α, interleukin (IL)-6, and IL-12, in macrophages are impaired both in vivo and in vitro. Administering exogenous leptin upregulates both phagocytosis and proinflammatory cytokine production in macrophages collected from ob/ob, but not from db/db, mice. These observations strongly suggest a physiological role of leptin in modulating inflammatory process.

In a cross-sectional investigation involving healthy young males, leptin was independently associated with C-reactive protein, a widely recognized marker of atherosclerotic vascular risk, although whether this is a causal association is unknown. At present, information regarding the interactions between leptin and various inflammatory reactions in humans is limited, but the proinflammatory actions of leptin are speculated to be involved in vascular remodeling.

**Prothrombotic Actions of Leptin**

Obese subjects appear to be predisposed to thrombosis formation, raising the risk of deep venous thrombosis and pulmonary embolism. Experimental evidence obtained with animal models suggests that leptin might be an important procoagulant factor. Thrombi originating from arterial lesions in ob/ob mice are unstable as compared with those in littermate controls. Platelet aggregation is blunted in ob/ob and db/db mice. Exogenous leptin normalizes thrombus formation and platelet aggregation in ob/ob, but not in db/db, mice. Bone marrow transplantation from db/db to normal mice delays thrombus formation in recipients, suggesting the importance of leptin signaling in platelets in thrombosis formation. Leptin accelerates thrombogenesis by acting on platelets of ob/ob mice after vascular injury in vivo. In addition, leptin modestly decreases the expression of thrombomodulin, an antithrombogenic protein, in cultured HUVECs. These prothrombotic actions of leptin might contribute to the elevated risk of developing acute coronary events, venous thrombosis, pulmonary thromboembolism, and thrombotic events after plaque rupture, in obese subjects.

**Prooxidant Actions of Leptin**

Increased oxidative stress has been recognized in experimental animal and human obesity and may contribute pathogenically to the metabolic syndrome. Numerous reports have shown that leptin increases oxidative stress via multiple mechanisms. In bovine aortic endothelial cells, leptin induces mitochondrial superoxide production by increasing fatty acid oxidation via activation of protein kinase A. In rats, leptin administration for 7 days decreased the activity of paraoxonase-1, an antioxidant enzyme contained in plasma lipoproteins, followed by increased plasma and urinary concentrations of isoprostanes, reflecting increased oxidative stress. By increasing oxidative stress and activating protein kinase C, leptin promotes secretion of atherogenic lipoprotein lipase from macrophages in vitro. Thus, leptin-induced oxidative stress is likely not only to directly damage endothelial and vascular smooth muscle cells but also to increase serum atherogenic factors, contributing to development of atherosclerosis.

Collectively, data from animal and human studies suggest that leptin plays major roles in the pathophysiology of obesity-related atherogenesis by impacting multiple steps, including vascular inflammation, proliferation, calcification, and elevated oxidative stress.

**Adiponectin**

Adiponectin, also termed Acrp30, apM1, AdipoQ, or GBP28, was identified independently by 4 research groups using different approaches, as a protein that is specifically and most abundantly produced in adipose tissue. It has a 20-residue signal sequence, collagen-like motif and globular domain and shows significant homology with collagens X and VIII and complement factor C1q. Adiponectin molecules combine via its collagen domain, producing a wide range of multimer complexes in plasma: a low-molecular-weight trimer, a middle-molecular-weight hexamer, and a high-molecular-weight 12- to 18-mer adiponectin.

Plasma adiponectin levels in humans are quite high, normally ranging from 3 to 30 μg/mL. In contrast to leptin, adiponectin plasma levels correlate negatively with body mass index. The negative correlation is stronger between plasma adiponectin levels and visceral adiposity than between this protein levels and subcutaneous adiposity. The expression of adiponectin in adipose tissue is reportedly regulated by several mechanisms via humoral and neuronal pathways. As an example, insulin and insulin-like growth factor-1 both upregulate adiponectin expression, whereas TNF-α and activation of the peroxisome proliferators-activated receptor (PPAR) have the opposite effect. Angiotensin II also reportedly reduces adiponectin production, as described below. In addition, sympathetic activation suppresses adiponectin expression via adrenergic β function. The mechanism underlying the adiponectin reduction in obese subjects remains unclear, but a plausible explanation is that inflammatory cytokines, eg, TNF-α, cause transcriptional suppression and secretory inhibition of adiponectin.

Different types of putative adiponectin receptors have been described. T-cadherin was identified as a receptor for the hexameric and high-molecular-weight species of adiponectin but for neither the trimeric nor the globular species. On the other hand, novel family proteins, designated AdipoR1 and AdipoR2, were found to be receptors for globular and full-length adiponectin. This family of adiponectin receptors is predicted to contain 7-transmembrane domains, despite being structurally and functionally distinct from G protein-coupled receptors. AdipoR1 is abundantly expressed in skeletal muscle, whereas AdipoR2 is expressed mainly in the liver. Very recently, simultaneous disruption of both AdipoR1 and -R2 was reported to abolish adiponectin binding as
well as its actions.65 The molecular pathways by which adiponectin mediates its effects apparently involve activation of AMP-activated protein kinase (AMPK), PPARα, and p38 mitogen-activated protein kinase signaling pathways,64 although further investigation is needed in this field.

**Adiponectin and Hypertension**

Lower concentrations of plasma adiponectin have been associated with essential hypertension. Patients with hypertension appear to have significantly lower plasma adiponectin levels than normotensive patients.65,66 The mechanism underlying this observation may involve the effects of angiotensin II. Infusion of angiotensin II in rats decreased plasma adiponectin levels via signaling through the angiotensin II type 1 receptor.58 Human subjects with essential hypertension, treated with angiotensin II receptor antagonists or angiotensin-converting enzyme inhibitors, had increased adiponectin concentrations without affecting body mass indices.67 However, the molecular mechanisms whereby angiotensin II signaling reduces adiponectin production have yet to be clarified.

**Adiponectin and Atherosclerosis**

Lines of evidence obtained from experimental animal models, such as adiponectin overexpression and knockout mice, have indicated protective effects of adiponectin against the development of obesity-related vascular diseases including atherosclerosis.

Adenovirus-mediated overexpression of adiponectin in apolipoprotein E (apoE)-deficient mice attenuates atherosclerotic lesion formation in the aortic sinus as compared with control apoE-deficient mice.68 Transgenic overexpression of globular adiponectin also ameliorates atherosclerotic lesion formation and diminishes the expression of the class A scavenger receptor in apoE-knockout mice, despite the absence of changes in blood glucose and lipid levels.69 These effects of adiponectin were confirmed by studies using adiponectin-knockout mice. Adiponectin-knockout mice show increased neointimal hyperplasia and proliferation of smooth muscle cells following acute vascular injury.70,71 Conversely, adenovirus-mediated reexpression of adiponectin blunts the increase in neointimal thickening observed in adiponectin-knockout mice.71 These in vivo experiments have demonstrated that adiponectin plays a role in preventing atherosclerotic progression. This conclusion appears to be supported by reports showing that, in humans, mutations and polymorphisms within the adiponectin gene, which are associated with lower adiponectin levels, are associated with coronary artery disease.72,73

Adiponectin expression in adipocytes and its plasma levels are upregulated by treatment with thiazolidinediones, agonists for PPARγ.74 There is mounting evidence that PPARγ agonists reduce the incidence of cardiovascular diseases, including myocardial infarction and stroke, in patients with type 2 diabetes who are at a high risk for macrovascular events.75 Adiponectin deficiency diminishes the ability of thiazolidinediones to improve glucose tolerance,76 suggesting involvement of adiponectin in the protective effects of thiazolidinediones against the development of cardiovascular diseases.

**Protective Role of Adiponectin Against Endothelial Dysfunction**

A series of in vitro and in vivo studies has suggested that adiponectin exerts protective actions on endothelial cells, thereby preventing the pathogenic effects of obesity on vascular function.

Adiponectin may exert antiinflammatory properties in part by altering NO levels in the endothelium. In human aortic endothelial cells, adiponectin promotes endothelial NO synthase mRNA and its protein expression, resulting in enhanced NO production via AMPK pathway activation.77,78 Globular adiponectin also reverses oxidized LDL-induced suppression of endothelial NO synthase activity.78,79 Adiponectin-knockout mice show impaired endothelial-dependent vasodilation when given an atherogenic diet.69 In addition, adiponectin has antiapoptotic effects on endothelial cells.80,81 Taken together, these observations indicate that adiponectin protects against endothelial dysfunction through multiple mechanisms.

Adiponectin also inhibits nuclear factor-κB (NF-κB) activation in both endothelial cells and macrophages. Inhibition of endothelial NF-κB signaling by adiponectin treatment suppresses TNF-α-stimulated expression of the proinflammatory cytokine IL-8 as well as adhesion molecules, including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, such that the attachment of monocytes to endothelial cells is attenuated.82,83 Adiponectin-induced suppression of these adhesion molecules was also demonstrated in vivo with adenovirus-mediated overexpression of adiponectin in apoE-deficient mice.69 In addition, in macrophages as well, adiponectin suppresses NF-κB signaling84,85 and the expression of class A scavenger receptors, resulting in reduced foam cell formation and the secretion of proinflammatory cytokines.86 Foam-cell formation is further reduced by adiponectin-induced downregulation of acyl-coenzyme A:cholesterol acyltransferase-1, the enzyme that catalyzes the formation of cholesteryl esters,87 in macrophages. Adiponectin also enhances expression of the antiinflammatory cytokine IL-10 and the tissue inhibitor of metalloproteinase-1 in macrophages.88 Through this variety of mechanisms, adiponectin limits the initiation of atherosclerotic plaque formation.

**Protective Role of Adiponectin Against Vascular Remodeling**

The evolution of a fatty streak into a complex lesion is characterized by the proliferation of smooth muscle cells, their migration toward the intima, and their synthesis of collagen. Adiponectin may modulate smooth muscle cell proliferation during the development and progression of vascular lesions. Physiological concentrations of adiponectin significantly suppress both proliferation and migration of human aortic smooth muscle cells in vitro, induced by platelet-derived growth factor-BB, via direct binding with platelet-derived growth factor-BB.89 Adiponectin was also shown to generally inhibit growth factor-stimulated extracellular signal-regulated kinase signaling. Similarly, adiponectin was found to inhibit smooth muscle cell proliferation through its ability to bind to various growth factors and to interfere...
with receptor-mediated cellular responses. As described above, these effects of adiponectin were confirmed by in vivo studies with adiponectin-knockout mice. Thus, adiponectin may act as a modulator of vascular remodeling and may favor plaque stabilization via these various mechanisms.

**Protective Role of Adiponectin Against Thrombosis Formation**

Investigations using adiponectin-knockout mice further revealed adiponectin to potentially be an endogenous anti-thrombotic factor. Compared with wild-type control mice, adiponectin-knockout mice showed enhanced thrombus formation and platelet aggregation at sites of vascular injury, with no differences in either platelet counts or coagulation parameters. Adenovirus-mediated supplementation of adiponectin bluntely this enhanced thrombus formation. The antithrombotic actions of adiponectin might well play a protective role against developing acute coronary events and some thrombotic diseases.

**Role of Adiponectin in Protection From Ischemic Heart Disease**

Obesity-related disorders have a major impact on both the incidence and the severity of ischemic heart disease, and adiponectin may have a protective function in this setting. Adiponectin treatment inhibits apoptosis of cardiac myocytes and fibroblasts exposed to hypoxia-reoxygenation stress. Blockade of the AMPK pathway by dominant-negative AMPK expression inhibits this adiponectin effect of protecting against apoptosis. In addition, cyclooxygenase-2 is up-regulated by adiponectin, leading to increased prostaglandin E2 synthesis. Adiponectin thus appears to protect against myocardial ischemia/reperfusion injury through AMPK-dependent and cyclooxygenase-2–dependent pathways. In adiponectin-knockout mice, larger infarcts are observed after ischemia/reperfusion, which is associated with greater myocardial cell apoptosis and TNF-α expression. Adiponectin replenishment attenuates these damaging effects. Thus, adiponectin may protect myocardial cells from hypoxic stress via both antiapoptotic and antiinflammatory mechanisms. Therefore, adiponectin administration might have a practical clinical application in the treatment of acute myocardial infarction.

**Other Adipocytokines**

**Tumor Necrosis Factor α**

The first clear links among obesity, insulin resistance, and chronic inflammation were provided by a report showing enhanced expression of TNF-α, a proinflammatory cytokine, in adipose tissue of obese mice. Lack of TNF-α function improves insulin resistance in obese mice, suggesting an important role for TNF-α in the development of insulin resistance. TNF-α is suggested to be involved in vascular remodeling via proinflammatory and insulin resistant effects. Interestingly, obesity is associated with macrophage accumulation in adipose tissue, and TNF-α is apparently derived from infiltrating macrophages, suggesting macrophage infiltration of adipose tissue to play a role in development of obesity-related morbidities.

**Plasminogen Activator Inhibitor-1**

PAI-1 is another adipocytokine, which is highly expressed in adipose tissue and has thrombotic effects. During progressive fat accumulation, PAI-1 expression is markedly enhanced in visceral adipose tissue. Plasma PAI-1 levels correlated significantly with visceral adiposity, as evaluated by computed tomography scanning, in humans. Therefore, PAI-1 secreted from accumulated visceral adipose tissue might play an important role in the development of thrombotic disorders, ie, the ultimate consequences of atherosclerosis.

**Retinol-Binding Protein 4**

In subjects with obesity and type 2 diabetes, GLUT4 glucose transporter expression is selectively decreased in adipocytes. Conversely, adipose-specific GLUT4 disruption secondarily induces insulin resistance in muscle and liver. In this mouse model, RBP4 was identified as an upregulated protein in adipose tissue. Transgenic expression or injections of RBP4 caused insulin resistance in mice, whereas experimentally decreasing RBP4 levels ameliorated insulin resistance in diet-induced obesity. RBP4 enhances hepatic gluconeogenesis and attenuates insulin signaling in skeletal muscle. Serum RBP4 is elevated in insulin-resistant mice and humans with obesity and type 2 diabetes. Thus, RBP4 might play a major role in the development of insulin resistance, although the impact of RBP4 on obesity-related hypertension and vascular diseases remains uncertain.

**Resistin**

Resistin is a member of the newly recognized family of cysteine-rich secretory proteins called resistin-like molecules (RELMs) or FIZZ (found in the inflammatory zone). Resistin is expressed almost exclusively in white adipose tissue and leads to insulin resistance in mice. A few studies focusing on the link between resistin and endothelial functions have recently been published. Resistin promotes endothelin-1 release and also upregulates the expressions of adhesion molecules, monocyte chemoattractant chemokine-1, and pentraxin 3, a marker of NF-κB–dependent inflammation, while downregulating the expression of TNF-receptor–associated factor-3, an inhibitor of CD40 ligand signaling in endothelial cells. These results suggest that resistin contributes to initiation or perpetuation of the atherosclerotic state. However, unlike murine resistin, human resistin expression is very low in adipocytes while being readily detectable in mononuclear blood cells. Therefore, the role of resistin in the development of obesity-related vascular diseases in humans is still uncertain.

**Humoral Factors Derived From the Liver**

In addition to adipocytokines, circulating factors secreted by the liver are also involved in systemic metabolic regulation. Members of the angiopoietin-like (Angptl) family of proteins are structurally related to angiopoietins, although their receptors are currently unknown. Angptl3 and Angptl6 (angiopoietin-related growth factor) expressions are restricted mainly to the liver, whereas Angptl4 expression is most abundant in the liver and adipose tissue. Angptl3, -4, and -6
are detected in the systemic circulation, suggesting an endocrine function.

Like the angiopoietins, these Angptl proteins play important roles in angiogenesis, but there are also several reports showing their involvement in triglyceride and energy metabolism as well as insulin sensitivity. Angptl3, a downstream target of the oxysterol receptor liver X receptor, is involved in development of the hypertriglyceridemia. The underlying mechanism appears to be reductions in very-low-density lipoprotein clearance secondary to lipoprotein lipase inhibition and direct activation of lipolysis in adipocytes. In contrast, Angptl6 is suggested to function in counteracting obesity and related insulin resistance through increased energy expenditure.

Angptl4 is also expressed mainly in the liver and adipose tissue, and its expression changes with nutrition status and also according to the activation state of PPARs. Adenovirus-mediated expression of Angptl4 potently decreased blood glucose and improved glucose tolerance, whereas it induced hyperlipidemia, fatty liver, and hepatomegaly. In addition, in patients with type 2 diabetes, serum Angptl4 were lower than in healthy subjects.

Thus, the function, or even dysfunction, of pathways mediated by these humoral factors derived from the liver may contribute to the development of hyperlipidemia and insulin resistance, both major elements of the metabolic syndrome. However, further intensive studies are needed to elucidate the contributions of these factors to cardiovascular disease.

Neuronal Signals From Intraabdominal Tissues in Response to Metabolic Alterations

In addition to humoral pathways, autonomic nervous system is likely to play an important role in both metabolic and cardiovascular regulation. The central nervous system (CNS) integrates signals from peripheral sites, thereby modulating glucose and energy metabolism as well as blood pressure. At least 2 avenues for these signals, humoral and neuronal, are involved in the underlying mechanisms. Whereas humoral signals including adipocytokines have been intensively investigated in recent years, neuronal signals from adipose tissue and the liver remain largely a mystery. Several recent reports, including ours, have indicated the importance of afferent neuronal signals in response to metabolic alterations, such as adiposity, in intraabdominal organs/tissues. In this regard, afferent signals from intraabdominal organs transmitted by autonomic neurons have attracted considerable attention. Organs/tissues communicate metabolic information each other via humoral and neuronal pathways (Figure 2).

Neuronal Signals From Adipose Tissues

Fat pads have rich sympathetic fiber innervation. Numerous studies have revealed a role for efferent sympathetic nerves in lipolysis. Various signals from the brain modulate the rate of lipolysis in adipose tissue via sympathetic action. In contrast, only a few studies have examined afferent nerve signals from adipose tissue. According to these reports, activation of afferent nerves from intraabdominal (epididymal) adipose tissue results in reflex signals being sent to white adipose tissues via efferent sympathetic nerve activation. The functional significance of these afferent signals, however, was not clarified. Research performed by our group has suggested that neural afferent signals from intraabdominal adipose tissue to the brain affect hypothalamic leptin sensitivity, thereby modulating food intake and sympathetic outflow.

Our goal was to determine whether a local reduction in the adiposity of intraabdominal adipose tissue would reverse obesity-related metabolic disorders, in particular, insensitivity to leptin and insulin. Therefore, adenoviral-mediated expression of uncoupling protein (UCP)1, which functions to dissipate energy as heat, was attempted in epididymal adipose tissue of diet-induced obese and diabetic mice in which insulin and leptin resistance had already developed. Despite UCP1 being expressed in epididymal adipose tissue at only very low levels, food intake clearly declined in association with decreased serum leptin levels as well as downregulation of orexigenic neuropeptide Y and upregulation of the anorexigenic precursor neuropeptide proopiomelanocortin in the
hypothesizes. The response to exogenous leptin was enhanced in these mice. In addition, hypophagia could not be duplicated in ob/ob mice with mutant leptin receptors. Collectively, these findings convincingly demonstrate that very limited UCP1 expression in the intraabdominal fat pad dramatically ameliorates the hypothalamic leptin resistance induced by high-fat-diet feeding. Local dissection of nerves from the epididymal fat pad as well as pharmacological deafferentation abrogated the anorectic effects of adipose UCP1 expression. Taken together, our results suggest afferent nerve signals originating in epididymal fat pads to modulate hypothalamic leptin sensitivity.

Hypothalamic leptin resistance is an important mechanism that maintains the obese state. Therefore, the perturbation of the afferent signals from adipose tissue might contribute to the development of obesity-related disorders, including hypertension and atherosclerosis. Adipose UCP1 expression increases sympathetic outflow, also suggesting the effects of adipose tissue-derived afferent signals on vascular systems. Adipose tissues were long recognized as passive energy storage sites. The discovery of various adipocytokines has raised adipose tissue to the status of a versatile endocrine organ. The aforementioned recent studies may provide additional evidence of the key role of adipose tissue as an important base from which neuronal signals originate. Further elucidation of this new pathway could open a new paradigm enhancing our understanding of adipose functions and dysfunctions, and thereby the pathophysiology of vascular diseases.

Neuronal Signals From the Liver
Nutrients absorbed from the gut enter the portal vein, a major route to the liver, thereby reaching the liver directly. Thus, given its anatomical location, it seems reasonable for the liver to function as a nutrient sensor and to send signals that regulate systemic metabolism. Signals regarding serum glucose levels from the so-called hepatoportal glucose sensor to the brain have been demonstrated to be carried along afferent vagal nerve pathways. Raising portal vein glucose levels decreases vagal afferent discharges reaching the nuclei of solitary tract neurons, which in turn activates sympathetic efferents to the adrenal glands, liver, splanchnic bed, and pancreas. Because these reflex effenter outputs are all blocked by hepatic vagotomy, it appears that signals triggered by high levels of portal glucose are transmitted through vagal afferents. Similarly, hepatic portal infusions of linoleic acid raised hepatic vagal afferent activity, suggesting hepatic vagal afferent involvement in the transmission of signals regarding lipid metabolism to the CNS. In addition, infusion of long-chain fatty acids into the portal vein activates the sympathetic nervous system, thereby elevating blood pressure. Therefore, portal nutrient signals may influence systemic blood pressure through afferent vagal and efferent sympathetic nerves. Our recent study provided further evidence of the link between hepatic metabolism and peripheral adiposity through an autonomic nerve circuit consisting of afferent vagal and efferent sympathetic nerve activity.

Hepatic expression of PPARγ, especially PPARγ2, has been shown to be functionally enhanced in a number of obesity models. Therefore, to identify the mechanism underlying the interorgan/tissue communications between the liver and peripheral tissues, including muscle and fat, we overexpressed PPARγ2 in the livers of mice and produced hepatic steatosis using adenoviral gene transfer. Contrary to the increased adiposity in the liver, hepatic PPARγ2 expression markedly reduced adiposity in the periphery with enhanced lipolysis. Systemic metabolic rates were increased, and peripheral insulin sensitivity and glucose tolerance were thus markedly improved. These remote effects were attributed to increased sympathetic outflow into muscle and adipose tissues. Selective hepatic branch vagotomy and pharmacological deafferentation of the vagus completely reversed these remote effects. Thus, hepatic PPARγ2 expression and/or hepatic lipid accumulation stimulates afferent vagal nerve fibers, communicating metabolic information to the brain and producing antiobesity and antiinsulin-resistant effects in muscle and adipose tissue via efferent sympathetic pathways. Fat storage in the liver changes dynamically in accordance with the systemic energy balance and is associated with several features of the metabolic syndrome. Because hepatic PPARγ expression is physiologically associated with obesity, these findings indicate that the liver transmits information regarding excess energy to the CNS via the afferent vagus. When the brain receives this information regarding excess energy storage mediated by leptin from adipose tissues and via the afferent vagus from the liver, the sympathetic nervous system is activated, which in turn enhances energy expenditure and lipolysis, thereby maintaining energy homeostasis. Notably, liver-specific disruption of PPARγ in ob/ob mice prevented hepatic steatosis but increased peripheral adiposity, resulting in aggravation of the diabetic phenotype attributable to decreased insulin sensitivity in muscle and fat. Thus, this system consisting of an autonomic nervous circuit appears to function as a protective mechanism against excess calorie intake in physiological settings.

A similar autonomic nerve circuit appears to play an essential role in development of glucocorticoid-induced insulin resistance and hypertension. Glucocorticoid excess is well known to result in insulin resistance and hypertension. In particular, accelerated conversion of glucocorticoid from the inactive to the active form in adipose tissue has phenotypic similarities with the metabolic syndrome. In mice, chronic glucocorticoid exposure leads to insulin resistance and hypertension associated with increased sympathetic tone, renal activity, and urinary sodium retention. The underlying mechanism involves hepatic activation of PPARα. Deafferentation, whether surgical or pharmacological, of the hepatic vagus reversed these phenotypic features following chronic glucocorticoid exposure. Taken together, these observations indicate the importance of the vagal afferent pathway in regulating insulin sensitivity and blood pressure. The development of hypertension is attributable to sympathetic activation. Thus, autonomic nerve circuit consisting of hepatic vagal afferent and sympathetic efferent nerves may contribute to the development of obesity-related hypertension. Elucidation of the molecular mechanisms, including the mediators influencing vagal activity, could lead to new therapeutic
approaches to the metabolic syndrome and cardiovascular diseases.

Conclusion
There is a growing body of evidence for a link between obesity and cardiovascular diseases, such as hypertension and atherosclerosis. During this decade, the versatility of adipose tissue as an endocrine organ and as a contributor to disease development has been established. Adipocytokine-mediated crosstalk between adipose tissue and the vascular system is clearly important. In addition, a number of recent studies have shown that tissue-specific knockout mice exhibit unexpected phenotypes, suggesting the presence of currently unknown crosstalk among organs/tissues. Further unraveling the complexities of this interorgan communication would enhance our understanding of the development of obesity-related disorders. Metabolism is not an independent process, segregated among different organs/tissues, but rather is coordinated and regulated throughout the body. Metabolic regulation coordinated among organs/tissues, which requires communication among these organs/tissues, is apparently essential for maintaining the homeostasis of systemic metabolism, particularly glucose and energy metabolism. Therefore, perturbation of this coordinated control system may lead to the development of metabolic disorders. Recent research advances in this field have revealed myriad complex and important roles of the CNS. The brain receives various forms of metabolic information from peripheral organs/tissues through humoral and neuronal avenues (Figure 3). For instance, leptin acts on the hypothalamus and other brain areas, mediating divergent effects on lipid metabolism and insulin signaling in the brain.\(^\text{137}\) Adiponectin also appears to exert central effects on energy metabolism.\(^\text{138}\) These inputs are probably integrated and processed in the brain, leading to the transmission of regulatory signals, which in turn induce appropriate systemic responses. In addition, humoral and neuronal signals affect each other, as exemplified by the findings that leptin and adiponectin expressions are regulated by sympathetic activity.\(^\text{23,60}\) Further elucidation of these regulatory systems, in much greater detail, may facilitate unraveling the mechanisms underlying metabolic homeostasis and thereby reveal the mechanisms underlying the development of the metabolic syndrome as a state of dysregulation (Figure 2). Moreover, targeting of the coordinated regulatory system consisting of these humoral and neuronal pathways is a potential therapeu-

tic strategy for obesity-related disorders, including cardiovascular diseases.

Sources of Funding
This work was supported by grant-in-aids for scientific research from the Ministry of Education, Science, Sports and Culture of Japan (B2, 18390267 to H.K.; and B2, 17390258 to Y.O.), by a grant-in-aid for scientific research from the Ministry of Health, Labor and Welfare of Japan (H16 genome-003 to Y.O.), and by the 21st Century Center of Excellence Programs of the Ministry of Education Science, Sports and Culture of Japan (to H.K. and Y.O.).

Disclosures
None.

References


Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced apoptosis by the high molecular weight form of adiponectin.

Katagiri et al Adiposity and Cardiovascular Disorders 37


Adiposity and Cardiovascular Disorders: Disturbance of the Regulatory System
Consisting of Humoral and Neuronal Signals
Hideki Katagiri, Tetsuya Yamada and Yoshitomo Oka

doi: 10.1161/CIRCRESAHA.107.151621

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/101/1/27

An erratum has been published regarding this article. Please see the attached page for:
http://circres.ahajournals.org//subscriptions/

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/
In an article by Katagiri et al (Circ Res. 2007;101:27–39), the authors incorrectly cited reference 4. The correct reference appears below. The corrected article is now available at http://circres.ahajournals.org.