MINIREVIEW

Adipokines and Coronary Vasomotor Dysfunction

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Research in the last 10–15 years has shown that fat cells (adipocytes) produce and release proteins with specific biologic activities. These proteins, termed adipokines, include the hormones leptin, adiponectin, and resistin. Adipose tissue is now recognized as an active endocrine organ. With the obesity pandemic swelling in the Western world, ongoing research is aimed at determining the biologic links between obesity and cardiovascular disease. This review presents basic historical background information on the major adipokines, introduces findings from clinical studies associating adipokines with cardiovascular disease, and summarizes results from recent basic science research studies of mechanisms of adipokine-induced cardiovascular dysfunction. Particular emphasis is placed on the action of adipokines in the coronary circulation—especially effects of adipokines on endothelial function, as endothelial damage is likely a critical event initiating atherosclerotic coronary artery disease. Exp Biol Med 232:727–736, 2007

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Introduction

Obesity is pandemic in Western society. Currently approximately 100 million Americans are overweight (body mass index >27 kg/m^2) or obese (body mass index >30 kg/m^2) (1). The pandemic is largely attributable to the adoption of a sedentary lifestyle coupled with the high availability of foods with high caloric content in Western cultures. These factors, superimposed on dated hunter-gatherer genotypes, have given rise to the modern-day global obesity epidemic (2).

For more than a century the burden of obesity has been documented in medical literature and textbooks. By the 1920s obesity was recognized as a major source of morbidity and mortality in Western society. In the 1928 edition of *Cecil's Textbook of Internal Medicine*, obesity was clinically defined as "a state in which the amount of fat stored in the body is excessive." Also, the text referenced data from life insurance companies conclusively demonstrating an association between obesity and shortened life expectancy; however, the mechanisms by which obesity led to early mortality remained elusive at the time. Curiously, no mention of an association between obesity and cardiovascular disease was noted with the exception of a modest elevation in arterial pressure that tended to decrease with weight loss. It was, however, clear at the time that obesity conferred a predisposition for type 2 diabetes upon those afflicted (3).

By 1950 obesity was known to markedly burden the cardiovascular system, but most clinical studies to date had only examined the anatomic, nutritional, metabolic, and endocrine aspects of the disease (4). Around the same time heart disease became the number one killer in the United States. As a result, approximately 50 years ago the United States Public Health Service started a large-scale study to investigate cardiovascular disease. Framingham, Massachusetts, was selected as a study site from which a large cohort of men and women was selected and followed (5). The study soon led to the identification of a number of

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modifiable risk factors for heart disease including obesity. The impact of obesity, especially when the associated glucose intolerance and hypertension were considered, on the incidence of coronary artery disease was staggering (5). Medicine was forever changed and a revolution in discovery resulted, as obesity and adipose biology have become major themes in contemporary clinical and scientific investigation. Thus, a clear association between obesity and coronary artery disease has materialized and fueled the discovery and study of several fat-derived hormones (adipokines) and their effects on cardiovascular tissues.

A major advancement in our understanding of adipose biology came with the cloning of the mouse obesity gene (*ob*) and its human homolog in 1994 (6). The product of the *ob* gene, leptin, was initially implicated in regulation of energy balance and metabolism (7). However, in recent years much attention has been given to elucidating the effects of leptin on the cardiovascular system. Since the discovery of leptin, other adipokines, including resistin and adiponectin, have emerged as potential players in the pathogenesis of cardiovascular disease in the overweight and obese. Additionally, the acute-phase reactants tumor necrosis factor α (TNF-α) and plasminogen activator inhibitor-1 (PAI-1) have evolving roles in the pathogenesis of vascular disease; however, the focus of this survey will be on the roles of leptin, adiponectin, and resistin in coronary vasomotor function.

It is the intent of this review to specifically summarize the coronary vascular effects of the aforementioned molecules based on the current literature.

Leptin

As mentioned above, a major breakthrough in obesity research came with the cloning of the mouse *ob* gene and its human homolog in 1994 (6). The product of the *ob* gene was thought to be a signal from adipose tissue that regulates the size of the body's fat stores (6). In 1998 Friedman (7) described the *ob* protein, leptin (from the Greek *leptos* meaning thin), as the product of a uniquely evolved physiologic system concerned with the regulation of fuel stores and energy balance. Mice possessing a mutation in the *ob* gene (*ob*/*ob* mice) exhibited obesity, type 2 diabetes, reduced activity, reduced metabolic rate, and reduced body temperature (8). It was later found that leptin is expressed and secreted predominantly in adipose tissue, making the molecule a so-called adipokine (9). It was postulated that fat stores send signals to the brain, which result in the reduction of food intake and increased energy expenditure. Additionally, *ob* expression was found to be elevated in obese humans, suggesting that increased adiposity results in hypersecretion of molecules involved in signaling the organism's energy status to the central nervous system (10). Modulation of sympathetic nervous tone is thought to be a major mechanism by which leptin controls energy expenditure (11–19).

Based on these studies, most consider leptin to be an antiobesity hormone due to its experimental effects on metabolism and food intake; however, according to a recent review by Ren (20), others argue that leptin has been inappropriately labeled as a hormone that minimizes weight gain in those exposed to an environment of readily available calories. Plasma leptin concentration is directly proportional to mean food intake over a period of days to weeks. Thus, it is hypothesized that a decrease in plasma leptin concentration serves as a short-term adaptation to starvation or famine (21). Reduced plasma leptin concentration results in decreased central sympathetic nervous outflow and mobilization of energy stores *via* stimulation of glucocorticoid secretion (22).

Since its discovery, leptin has gained much attention not only in endocrine and metabolism research but in cardiovascular science as well. Plasma leptin concentrations reported in normal, healthy humans are ~3–5 ng/ml, with concentrations in morbidly obese humans ranging as high as 90–95 ng/ml (18). Hyperleptinemia (elevated plasma leptin concentration), which is practically universal in obese humans (7), is an independent risk factor for cardiovascular disease (20). More specifically, elevated plasma leptin is a predictor of first myocardial infarction (23) and an independent risk factor for ischemic and hemorrhagic stroke (24). Accordingly, leptin has been deemed a component of the metabolic syndrome of obesity, insulin resistance, hypertension, and dyslipidemia; and high circulating plasma leptin levels are thought to play a role in the hastened development of coronary artery disease in obesity (25). Thus, there has been a strong impetus to study leptin among clinical and basic cardiovascular scientists.

Hyperleptinemia has been implicated in various biologic processes that are integral components of the pathogenesis of coronary artery disease. These processes include cytokine signaling (20) and the up-regulation of phagocytosis and production of proinflammatory cytokines such as TNF-α (26) and C-reactive protein (27), which exert proinflammatory effects on endothelial cells (28). Also, leptin has been shown to promote platelet aggregation and thrombosis in human obesity (29–31). A recent review by Beltowski (32) in *Atherosclerosis* nicely outlines the role of leptin in the pathogenesis of atherosclerosis. However, it must be noted that in spite of the mass of studies demonstrating that leptin may exert proatherogenic effects both *in vivo* and *in vitro* and several clinical studies suggesting that high plasma leptin concentration is associated with atherosclerosis, no direct evidence to date demonstrates a precise role for leptin in the pathogenesis of atherosclerotic disease (32).

In addition to studies dealing with atherosclerosis, the vasomotor effects of leptin have become the focus of ongoing research. Since its discovery, leptin has been shown to exert a variety of effects in many tissues, including vasomotor effects at various peripheral targets (33, 34). In the late 1990s leptin gained attention as an activator of the

sympathetic nervous system. It was shown that leptin not only stimulates central sympathetic nervous outflow (as cited above) but is also involved in regional sympathetic nerve activation (14). More specifically, many studies have demonstrated that leptin increases renal sympathetic nervous activity and raises peripheral vascular resistance and mean arterial pressure (11, 14, 17–19). Excellent reviews by Hall *et al.* and Haynes *et al.* (13, 15) in recent years nicely summarize the role of leptin in sympathetic nervous dysfunction, hypertension, and renal disease.

In 2000 a study by Kimura *et al.* (35) suggested that leptin is involved in nitric oxide–mediated endothelium-dependent vasodilation. Thus, a paradox arose in that leptin, which at the time had already been relatively extensively studied as a mediator of sympathetic-mediated increases in vascular resistance, was shown to be a mediator of vasodilation. Subsequent studies seemed to validate the hypothesis that leptin induces nitric oxide–dependent vasodilation (35–37). *In vitro* studies supported these findings, demonstrating that leptin induces nitric oxide release from human aortic endothelial cells *via* phosphorylation of Akt kinase at Ser 473 and Thr 308 and activation of endothelial nitric oxide synthase (eNOS) *via* phosphorylation at Ser 1177 (38, 39). Incongruently, others were finding leptin-mediated vasodilation to be nitric oxide independent (36, 40), with some convinced that both are partially true. The confusion was likely attributable in part to differences in species and technical experimental design. Also, the majority of these studies were conducted using very high (pharmacologic) concentrations of leptin that are well outside the reported physiologic and pathophysiologic plasma ranges; thus, the findings must be interpreted with caution. These studies were all conducted in noncoronary vascular beds.

A study in 2003 by Matsuda *et al.* (41) demonstrated that leptin-mediated coronary vasodilation in humans is nitric oxide independent. This finding was somewhat inconsistent in that epidemiologic studies had linked leptin to increased risk for myocardial infarction (23); however, it was the first study to analyze the direct effects of leptin on coronary vasomotor function. The subjects were all undergoing cardiac catheterization for angina, and some were diabetic and/or smokers; therefore, the findings should be interpreted cautiously when considering the physiologic effects of leptin on coronary vasomotor function in the healthy heart. Unfortunately, Matsuda *et al.* did not report myocardial oxygen consumption (or a clinically acceptable index thereof [e.g., pressure-rate product]) in their study. Thus, it is impossible to determine whether the demonstrated coronary vasodilatory effect of leptin was due to direct action at endothelial or vascular smooth muscle or simply the result of increased myocardial metabolic rate (e.g., *via* activation of the regional sympathetic nervous system). Furthermore, at the time of the Matsuda study the expression of leptin receptors in coronary arteries had not been studied.

A study by Knudson *et al.* (42) in 2005 aimed to further characterize the effects of leptin on coronary vasomotor function and attempted to resolve some of the disparities present in the literature. Using reverse transcriptase–polymerase chain reaction (RT-PCR) and immunocytochemistry analyses, Knudson *et al.* demonstrated that the long-form leptin receptor gene (*ObRb*) is expressed and signaling-competent long-form receptors are present in confluent cultures of human coronary artery endothelial cells. Additionally, RT-PCR analysis confirmed the expression of the *ObRb* gene in canine left circumflex coronary arteries (42). Leptin receptor gene expression had been previously demonstrated in human umbilical vein endothelial cells (43); however, the Knudson study was the first investigation to demonstrate expression of the leptin receptor gene and the presence of the signaling-competent leptin receptor protein in coronary arteries.

Additionally, Knudson *et al.* (42) demonstrated that high pharmacologic concentrations of leptin induce nitric oxide–dependent (inhibited by NG-nitro-L-arginine methyl ester [L-NAME] as well as endothelial denudation) vasodilation of pressurized coronary arterioles isolated from Wistar rats, lean Zucker rats, and normal mongrel dogs. This finding was consistent with other studies that had demonstrated that leptin induces vasodilation through eNOS; however, leptin-mediated coronary vasodilation was only observed at extremely high leptin concentrations. The normal range for plasma leptin in healthy humans is 3–5 ng/ml, and concentrations reported in obese humans are in the range of 8–90 ng/ml (18, 44, 45). Significant coronary arteriolar vasodilation was not observed until leptin concentrations reached approximately 160 ng/ml (10 nmol/L). Therefore, it is apparent that leptin-induced nitric oxide–dependent coronary vasodilation is a pharmacologic phenomenon that probably does not occur at physiologically or pathophysiologically relevant leptin concentrations. This hypothesis was tested by Knudson *et al.* (42) using open-chest dogs. Direct intracoronary infusion of leptin at physiologic and pathophysiologic concentration ranges had no effect on coronary blood flow, myocardial oxygen consumption, mean aortic blood pressure, or heart rate. To negate the possibility that leptin-mediated regional sympathetic activation (i.e., stimulation of alpha receptors on medium sized coronary arteries) masks nitric oxide–mediated coronary vasodilation, open-chest coronary blood flow experiments were also conducted in the presence of the ganglionic blocker, hexamethonium. As expected, since leptin alone had no hemodynamic effects, no changes from baseline in coronary blood flow, myocardial oxygen consumption, or systemic hemodynamics were observed when leptin was administered in the presence of sympathetic ganglionic blockade. Conclusively, despite the body of literature implicating leptin as an endothelium-dependent vasodilator, relevant concentrations of leptin probably have little direct effect on coronary blood flow or cardiac dynamics.

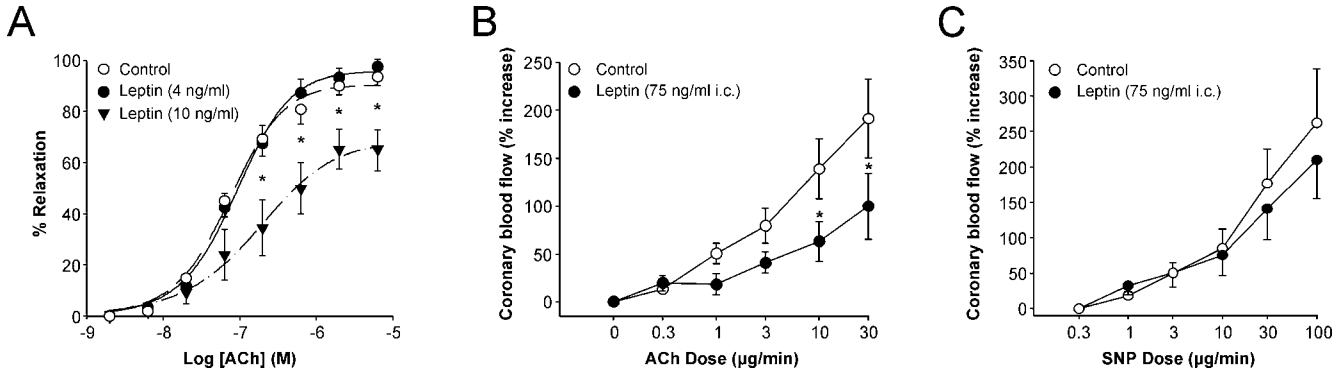

Figure 1. Leptin impairs acetylcholine-induced coronary artery relaxation of isolated canine coronary artery rings at a concentration of 10 ng/ml but not 4 ng/ml (Panel A). Leptin significantly reduced endothelial-dependent coronary vasodilation to acetylcholine in open-chest anesthetized dogs (Panel B) but did not affect endothelial-independent vasodilation to sodium nitroprusside (Panel C). Data from Knudson *et al.* (42) used with the permission of the American Physiological Society.

Of interest, Knudson *et al.* (42) also demonstrated that concentrations of leptin in the obese range impair acetylcholine-mediated coronary vasodilation in open-chest dogs and acetylcholine-mediated relaxation of isolated circumflex coronary artery rings (i.e., leptin induces significant coronary endothelial dysfunction acutely both *in vitro* [Fig. 1A] and *in vivo* [Fig. 1B]). Interestingly, lower (physiologic) concentrations of leptin had no effect on acetylcholine-mediated coronary artery relaxation either *in vitro* (Fig. 1A) or *in vivo* (Fig. 1B). In this study, leptin concentrations in the obese range did not affect endothelium-independent coronary vasodilation to sodium nitroprusside (Fig. 1C). Thus, the effect of leptin on coronary vasomotor responses was specific for endothelial-mediated dilation/relaxation. A study by Sundell *et al.* (46) examined coronary flow reserve in obese and nonobese subjects using positron emission tomography and demonstrated that serum leptin concentration is inversely related to adenosine-stimulated myocardial blood flow. These results suggest that leptin may have a role in reduced myocardial blood supply in obesity. These findings correlate with the plethora of epidemiologic studies linking leptin to risk for cardiovascular disease. The findings by Knudson *et al.* and Sundell *et al.* serve to strengthen the hypothesis that leptin is a key player in the pathogenesis of coronary atherosclerotic disease by way of mediating coronary endothelial dysfunction, which according to the Ross hypothesis (47) precedes overt atherosclerotic disease. Currently the precise mechanism(s) of leptin-mediated coronary endothelial dysfunction remains unknown.

Another study by Knudson *et al.* (48) demonstrated that prediabetic dogs, without histologic evidence of coronary atherosclerotic disease, are resistant to leptin-mediated coronary endothelial dysfunction. That is, acetylcholine-mediated coronary vasodilation is not changed by pathophysiologically relevant concentrations of leptin (48). This finding seems paradoxic; however, it may represent an early protective adaptive change in the pathogenesis of atherosclerosis. A recent study by Schindler *et al.* (49) in the *Journal of the American College of Cardiology* concluded that elevated plasma concentrations of leptin in obese patients may exert beneficial effects on the coronary endothelium to counterbalance the adverse effects of increases in body weight on coronary circulatory function. More studies are needed to test this hypothesis.

In summary, in the coronary circulation, leptin at physiologically relevant concentrations is not directly vasoactive; nonetheless, the long-form leptin receptor is present on human coronary endothelial cells and is expressed in dog coronary arteries. Further, concentrations of leptin in the obese range appear to have deleterious effects on coronary endothelial function and myocardial blood flow acutely; however, the mechanistic contribution of chronic hyperleptinemia to the initiation and development of coronary artery disease must be further explored.

Adiponectin

In 1996 a novel adipose-specific, collagen-like factor (initially termed adipose most abundant gene transcript 1 [apM1]) was cloned (50). Within a few years it was reported that obesity is associated with a paradoxic decrease in this adipose-specific protein; the normal plasma range in healthy humans being 1.9–17.0 mg/dl, with significantly lower levels reported in obese subjects (51). The protein was named adiponectin by Arita *et al.* (51) given its adipocyte origin and similarity in structure to other connective tissue proteins (e.g., collagen). Additionally, adiponectin levels are increased in anorexia nervosa (52). Thus, plasma adiponectin varies inversely with body fat content in humans.

Further characterization of the biologic role of adiponectin resulted in the demonstration of adiponectin release from adipocytes increasing in response to activation of peroxisome proliferator activator receptors (e.g., PPAR-γ) (53). The importance of adiponectin was most realized when it was demonstrated to be an insulin-sensitizing molecule (54–56). Further, it was demonstrated that the mechanism by which the insulin-sensitizing agents thiazolidinediones (TZDs, also known as "-glitazones") induce positive metabolic effects in type 2 diabetics is linked to an increase

in adiponectin levels (57). Although the precise mechanism by which TZDs increase adiponectin levels remains unclear, much is now known regarding the cellular effects of these agents (58). An excellent review by Ferre (59) outlines the proposed mechanisms of adiponectin release, with attention given to metabolic syndrome and PPAR-γ stimulation by TZDs. Another interesting review by Klein *et al.* (60) encompasses novel therapeutic strategies relating to adipose tissue targets.

The marked differences in plasma adiponectin concentrations between healthy and obese subjects stimulated interest in the molecule and the development of hypotheses regarding the role of adiponectin in the long observed, hastened development of vascular disease in obesity, metabolic syndrome, and type 2 diabetes. As with leptin, epidemiologic studies stratifying the risk of vascular pathology attributable to adiponectin ensued. Low plasma adiponectin concentrations (hypoadiponectinemia) are an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain (61). Also, decreased circulating adiponectin levels in obesity are associated with an increased risk of coronary artery disease (62–65) and myocardial infarction (66). Additionally, adiponectin is linked to future coronary events in men with type 2 diabetes (67). Hypoadiponectinemia is also associated with platelet activation in carotid atherosclerosis (68). Interestingly, unlike leptin, adiponectin may not be associated with an increased risk of cerebrovascular accident (69).

Given the multitude of studies linking adiponectin to cardiovascular disease, adiponectin replacement therapy holds promise in the treatment of metabolic syndrome and obesity. Many studies have examined the effects of raising adiponectin levels in those at risk for cardiovascular disease and events, most of which have employed TZD therapy as a means of increasing circulating adiponectin levels. Such studies have demonstrated that pioglitazone increases adiponectin and subsequently reduces TNF-α levels in type 2 diabetic patients (70); adiponectin delivered *via* an adenovirus vector reduces blood pressure in adiponectin-deficient, obese, KKAγ, and adiponectin knock-out mice (71); rosiglitazone therapy increases adiponectin levels and high-density lipoprotein cholesterol levels while reducing C-reactive protein, interleukin 6 (IL-6), IL-18, and plasma triglycerides in humans with metabolic syndrome (72, 73). A recent review by Han *et al.* (74) does an excellent job of describing the beneficial vascular and metabolic effects of PPAR activators. When reviewing these results, one cannot ignore the prospective therapeutic benefits of increasing plasma adiponectin in obese patients with metabolic syndrome and vascular disease. However, the mechanisms by which adiponectin provides improvement in, or in some cases reversal of, many features of metabolic syndrome have not been clearly defined. Some evidence points toward the anti-inflammatory effects of adiponectin (see below).

The precise role of adiponectin in the pathogenesis of vascular disease is likely complex and much remains to be delineated. Chronic inflammation is a recurring theme in metabolic-mediated vascular disease. As discussed previously, leptin exerts many pro-inflammatory effects; conversely, adiponectin is associated with induction of anti-inflammatory cytokine production (IL-10 and IL-1RA among others) (75). A study by Johns *et al.* in 2005 demonstrated that rosiglitazone therapy reduces E-selectin, P-selectin, and intercellular adhesion molecule 1 expression as well as leukocyte rolling in obese Zucker cremaster venules following ischemia-reperfusion injury (76). These anti-inflammatory effects may be linked to TZD-mediated increases in adiponectin. Thus, the chronic inflammation associated with vascular disease in obesity may be mediated in part by the loss of protective, adiponectin-mediated anti-inflammatory effects. It has also been shown that adiponectin plays a role in endogenous antithrombosis (77). Additionally, lowered adiponectin may be related to endothelial dysfunction in obese subjects. A study by Carmina *et al.* (78) demonstrated that obese women with polycystic ovary syndrome (PCOS) exhibit endothelial dysfunction that correlates with reduced insulin sensitivity and hypoadiponectinemia. Conversely, a recent study by Buras *et al.* (79) indicates that troglitazone-induced increases in adiponectin concentration are not associated with an improvement in endothelial function in the skin of diabetic humans. One plausible explanation for these disparate findings is differences in the pathophysiologies of PCOS and diabetes.

Most research to date includes characterization of the metabolic effects of adiponectin (much attention given to insulin resistance) and epidemiologic studies demonstrating that hypoadiponectinemia is a risk factor for cardiovascular disease and events of various types (as discussed above). Within the last year a few studies examining the role of adiponectin in coronary vasomotor function have been published. Epicardial adipose tissue produces adiponectin (80). Furthermore, in humans with coronary artery disease, there is a reduction in local epicardial adiponectin production (80). A study by Date *et al.* (81) using cardiac catheterization techniques measured adiponectin production across the coronary circulation in 22 nondiabetic, healthy subjects with no evidence of coronary artery disease (angiographically normal arteries). Coronary flow reserve was estimated using a Doppler flow wire to measure flow velocities at baseline and maximal hyperemia. Blood samples were simultaneously drawn from the left coronary ostium and the great cardiac vein. The authors observed a significant correlation between coronary flow reserve and the transcardiac adiponectin gradient (i.e., great cardiac vein concentration minus left coronary artery concentration). Those subjects with higher transcardiac adiponectin gradients exhibited higher coronary flow reserves. The study results offer little insight into the precise mechanism of adiponectin-mediated increases in coronary flow reserve, but the data do raise interesting questions that will require further evaluation. Another recent study by Takano *et al.*

(82), using similar techniques as the Date study, found a positive correlation between transcardiac adiponectin gradient and acetylcholine-induced increases in coronary artery diameter—without a correlation between adiponectin gradients and coronary vasomotor responses to nitroprusside or isosorbide dinitrite. The authors concluded that adiponectin plays a role in coronary endothelial function (as assessed by acetylcholine-mediated coronary vasodilation). Of further interest, Takano *et al.* (82) also studied patient groups with coronary vasospastic angina and microvascular angina. These particular groups exhibited impaired coronary endothelial responses to acetylcholine as expected; however, there was no significant association between coronary endothelial responses and transcardiac adiponectin gradient in the diseased groups. Thus, there is correlative evidence that reduced local cardiac adiponectin production is not only present in individuals with coronary artery disease but may also play a mechanistic role in the associated coronary endothelial dysfunction.

The studies by Date *et al.* and Takano *et al.* provide evidence that adiponectin may play a role in coronary vasomotor dysfunction and the pathogenesis of coronary artery disease. To further understand the impact of reduced epicardial adiponectin production in coronary artery disease, studies examining the coronary vasomotor properties of adiponectin on healthy animals, as well as genetically altered animals, might prove helpful. Functional, cellular, and molecular studies in experimental models of obesity would also provide insight into the pathophysiologic mechanisms by which hypoadiponectinemia induces coronary vasomotor dysfunction, which thereby confers heightened risk for coronary artery disease.

Resistin

In 2001 Steppan *et al.* (83) described and named a unique, adipocyte-derived signaling molecule, resistin (for resistance to insulin). Plasma resistin concentration is reported to be in the range of 3–13 ng/ml in healthy subjects with levels approaching 40 ng/ml in obese individuals (84–86). Observations by Steppan *et al.* include (i) plasma resistin levels are decreased by rosiglitazone administration and increased in diet-induced and genetic forms of obesity, (ii) administration of an antiresistin antibody reduces blood sugar and improves insulin action in diet-induced murine diabetes, (iii) treatment of healthy mice with recombinant resistin impairs glucose tolerance and insulin action, and (iv) resistin administration impairs insulin-induced glucose uptake in adipocytes. Thus, resistin became a major candidate as a molecular link between adipose tissue (obesity) and metabolic syndrome. These observations proved to be reproducible in large part (85, 87), and resistin has become the target of much investigation dealing with the mechanisms of disease progression in obesity and insulin resistance.

In 2003 Verma *et al.* (88) conducted a study examining the vascular endothelial effects of resistin, so-called adipokine-endothelial cell interactions. Using cultured vascular endothelial cells, Verma *et al.* demonstrated that resistin activates vascular endothelium, causing release of endothelin-1 (by way of activation of the AP-1 site of the endothelin-1 gene promoter). Additionally, resistin treatment increased endothelial cell expression of vascular cell adhesion molecule 1 and monocyte chemoattractant chemokine 1. Thus, resistin, like leptin, exerts proinflammatory changes in vascular endothelium in experimental settings. As a result, resistin has become an inflammatory marker of atherosclerotic disease (89). However, unlike adiponectin, resistin's association with markers of inflammation appears to be independent of body mass index (90). Hence, resistin may play a prominent role in the pathogenesis of diabetes-related vascular disease in nonobese subjects. Interestingly, a recent study in the *American Journal of Cardiology* demonstrated that medical and surgical weight loss improves endothelial function without correlation to plasma resistin levels (91). As with leptin, initial hypotheses surrounding the framework of resistin biology may prove to be false. More studies are needed to define the role of resistin in the pathophysiology of metabolic and inflammatory vascular disease.

As outlined, resistin mediates insulin resistance in many models of obesity. Furthermore, resistin induces marked inflammatory changes in endothelial cell cultures. A recent study indicates that resistin levels are elevated in patients presenting with unstable angina and myocardial infarctions (both non-ST segment elevation myocardial infarction [NSTEMI] and STEMI) and that plasma resistin levels correlate moderately with future cardiovascular death in patients with documented coronary artery disease (92). However, only a few studies to date have examined the direct effects of resistin on the coronary circulation.

A recent study by Kougias *et al.* (93) demonstrated that treatment of porcine coronary arteries with biologically relevant concentrations (10 ng/ml and 40 ng/ml) of resistin impaired endothelium-dependent relaxation to bradykinin. The impaired relaxation was associated with a marked increase in superoxide anion production. These effects were reversed by the antioxidant seleno-L-methionine. Additionally, treatment of isolated, cultured porcine coronary endothelial cells with resistin resulted in decreased expression of eNOS mRNA levels and eNOS immunoreactivity. Kougias *et al.* also reported resistin-mediated inhibition (resistin treatment: 40 ng/ml) of coronary vasorelaxation to sodium nitroprusside and thus concluded that resistin adversely affects endothelium-independent vasorelaxation as well as coronary endothelial function. The results of the Kougias study implicate resistin as a prooxidant mediator of coronary endothelial dysfunction, suggesting a role for resistin in the early pathogenesis of inflammatory coronary endothelial dysfunction in the obese; however, all experiments have been conducted *in vitro*.

A subsequent study by Dick *et al.* (94) further

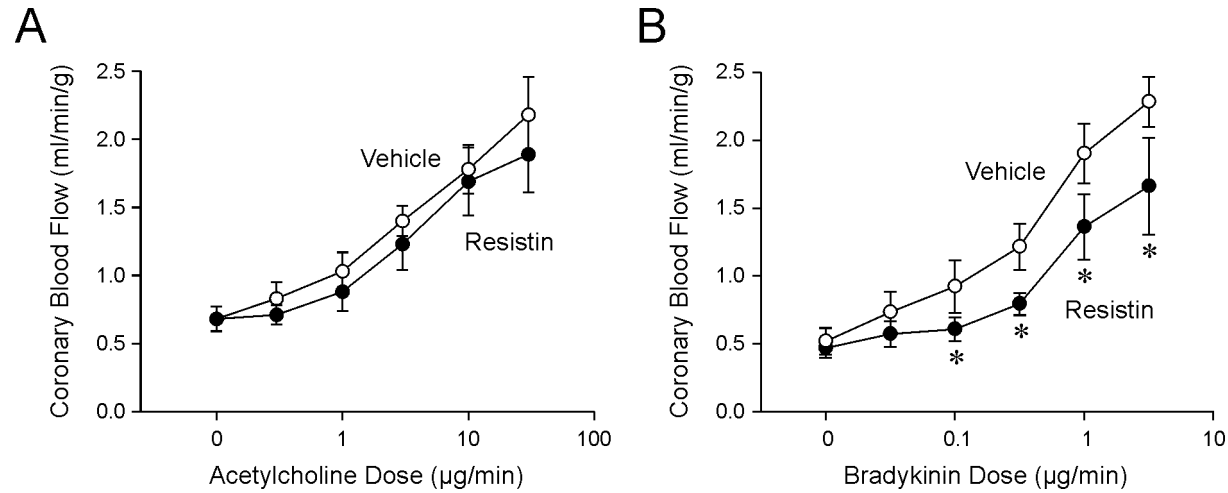

Figure 2. Resistin significantly attenuated coronary endothelial–dependent vasodilation to bradykinin (Panel B) but not to acetylcholine (Panel A) in open-chest anesthetized dogs. Data from Dick *et al.* (94) used with the permission of the American Physiological Society.

examined the effects of resistin on coronary vasomotor function both *in vitro* and *in vivo*. Dick *et al*. studied the hemodynamic effects of intracoronary administration of resistin in open-chest dogs, the effects of resistin on isolated coronary artery vasomotor responses to endothelium-dependent relaxants, and the effects of resistin on coronary artery superoxide anion production *in vitro*. Intracoronary administration of resistin did not significantly affect coronary blood flow, heart rate, or mean aortic blood pressure in open-chest, anesthetized dogs. In effect, resistin, like leptin, does not directly affect coronary vasomotor tone or systemic hemodynamics when infused into the canine coronary circulation. However, resistin did significantly attenuate coronary blood flow increases to intracoronarily administered bradykinin (Fig. 2B), while not affecting coronary vasodilation to acetylcholine (Fig. 2A). These results were validated *in vitro* as resistin significantly attenuated canine coronary artery relaxation to bradykinin but not acetylcholine. Thus, resistin, when administered acutely, causes significant coronary endothelial dysfunction *in vivo* and *in vitro*. Bradykinin elicits coronary vasodilation in dogs *via* the production of nitric oxide and other vasoactive substances including prostaglandin I_2 and endothelium-derived hyperpolarizing factors (EDHFs) (95). Since resistin-mediated attenuation of bradykinin-induced coronary vasodilation persisted in the presence of L-NAME and indomethacin, Dick *et al*. concluded that the inhibitory effect of resistin is likely mediated through EDHF(s) or other paracrine mediators. Further studies are needed to address this hypothesis.

In contrast to findings by Kougias *et al*., Dick *et al*. found that resistin treatment (10 ng/ml and 40 ng/ml) had no effect on superoxide production in isolated canine coronary arteries. Potential explanations for these disparate observations include species variation and size of coronary arteries used in isometric tension studies. Additionally, Dick *et al*. demonstrated that resistin-mediated impairment of bradykinin-induced coronary vasodilation persisted in the presence of L-NAME and indomethacin. Thus, alterations in eNOS expression/signaling do not appear to play a part in the resistin-mediated endothelial dysfunction observed in canine coronary circulation. Species differences (porcine vs. canine), differing resistin treatment times (10 mins in the Dick study and 24 hrs in the Kougias study), or differences in experimental design (vasomotor pharmacology experiments on isolated arteries in the Dick study and molecular biology experiments on cell cultures in the Kougias study) are probable explanations for the different observations.

Taken together, the studies by Kougias *et al*. and Dick *et al*. demonstrate that resistin alters coronary vasomotor responses *in vivo* and *in vitro*. Although differences in results were present, resistin impaired coronary vasorelaxation to bradykinin in both porcine and canine coronary circulations. With evidence increasing, more studies defining the mechanistic role(s) of resistin in coronary physiology and disease may prove beneficial in advancements in pharmacotherapeutics.

Conclusion

Although it has been documented in medical texts for decades that obesity is a major source of morbidity and mortality, the mechanisms of obesity-related cardiovascular dysfunction and pathology have largely remained elusive until recent years.

Much attention has been given to the chronic inflammatory state that accompanies obesity and metabolic syndrome. The focus of this review is the coronary vascular effects of adipokines. Although metabolic syndrome and type 2 diabetes were mentioned several times throughout, a recent review by Matsuzawa (96) discusses adipocytokines in the context of metabolic syndrome in much greater detail. A recent study by Picchi *et al*. (97) addressed the effects of TNF-α on coronary arteriolar endothelial function in animal

models of obesity and metabolic syndrome. Picchi *et al*. concluded that TNF-α administration induces endothelial dysfunction (abrogates endothelial-dependent dilation or coronary arterioles isolated from hearts of obese Zucker rats). This result implicates inflammatory cytokines as mediators of coronary dysfunction in obesity; however, with this hypothesis in its infancy, confirmation of the findings by Picchi *et al*. and others will be necessary for validation.

In recent literature, leptin, adiponectin, and resistin have all been implicated in coronary endothelial dysfunction. The balance of these hormones appears to be crucial for the maintenance of coronary endothelial function. The insulin-resistant state clearly results in the perturbation of leptin, adiponectin, and resistin levels in the blood. Interestingly, studies to date have demonstrated that these three adipokines are each potentially involved in the pathogenesis of coronary artery vasomotor dysfunction, although mechanisms by which these adipokines exert ill effects on the coronary vasculature differ. Leptin and adiponectin appear to be involved in pathways downstream from the acetylcholine receptor. Although not a mediator of physiologic coronary vasodilation, the muscarinic vasodilation pathway is an accepted means of assessing endothelium-dependent vasodilation. Resistin, on the other hand, affects coronary endothelial function from a different angle (the bradykinin pathway).

In conclusion, disruption of physiologic adipokine plasma levels and perturbations in adipokine signaling within the coronary vascular wall culminates in coronary endothelial dysfunction. Thus, alterations in adipokine biology may be a major precipitating factor in the initiation of coronary artery disease in individuals with metabolic disease.

With the incidence of obesity and insulin resistance climbing in Western populations, studies aimed at further characterizing the mechanisms of adipokine-mediated effects on coronary endothelial function are needed if we are to further understand the interplay between the endocrine function of adipose tissue and coronary vasomotor biology. Studies aimed at determining whether there is signaling interplay between adipokines (leptin, adiponectin, and resistin) at vascular targets would also be of interest. Additionally, other molecules receiving attention in obesity research (e.g., ghrelin, orexins, TNF-α) should be further studied with respect to the pathogenesis of coronary artery disease.

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