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Peptides Involved in Vascular Homeostasis

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Obesity and Cardiovascular Disease

Obesity has been classified as a major modifiable risk factor for cardiovascular diseases (CVDs) by the American Heart Association, as well as by the American College of Cardiology guidelines for secondary prevention of coronary artery disease (CAD) (Eckel and Krauss, 1998; Smith *et al.*, 2001). Obesity is related to the development of several different comorbidities such as hypertension, type 2 diabetes mellitus (T2DM) and dyslipidaemia, all well-documented risk factors for CVD, which cluster together as the metabolic syndrome (Eckel *et al.*, 2005). In this regard, regional fat distribution is particularly relevant to the development of the metabolic syndrome and its accompanying cardiovascular complications (Rodríguez *et al.*, 2007a). Upper-body obesity (i.e. visceral or 'android' obesity), as determined by an increased waist circumference and waist-hip ratio or elevated visceral fat area by image analysis at the lumbosacral level, is associated with an increased incidence of metabolic disturbances, elevated risk of CVD and premature death (Yusuf *et al.*, 2005; Kuk *et al.*, 2006).

Weight gain is accompanied by progressive physiological changes in cardiovascular function that can lead to heart failure (HF) (Kopelman, 2000). The increased lean and fat mass as well as body surface area characteristic of obesity determine an elevation in total blood volume, which, in turn, contributes to an increase in left ventricular (LV) preload and in resting cardiac output. The augmented demand for cardiac output is achieved by an increase in stroke volume, while the heart rate (HR) remains comparatively unchanged. The obesity-related increase in stroke volume results from an increase in LV diastolic filling. The elevated circulatory preload and afterload lead to LV dilatation (Fig. 9.1). An increased cardiac output is a common finding in moderate obesity, whereas not all obese individuals are hypertensive. In patients with raised systemic vascular resistance, the combination of obesity and hypertension results in a disproportionate increase in LV wall dimensions to the chamber radius, which leads to LV

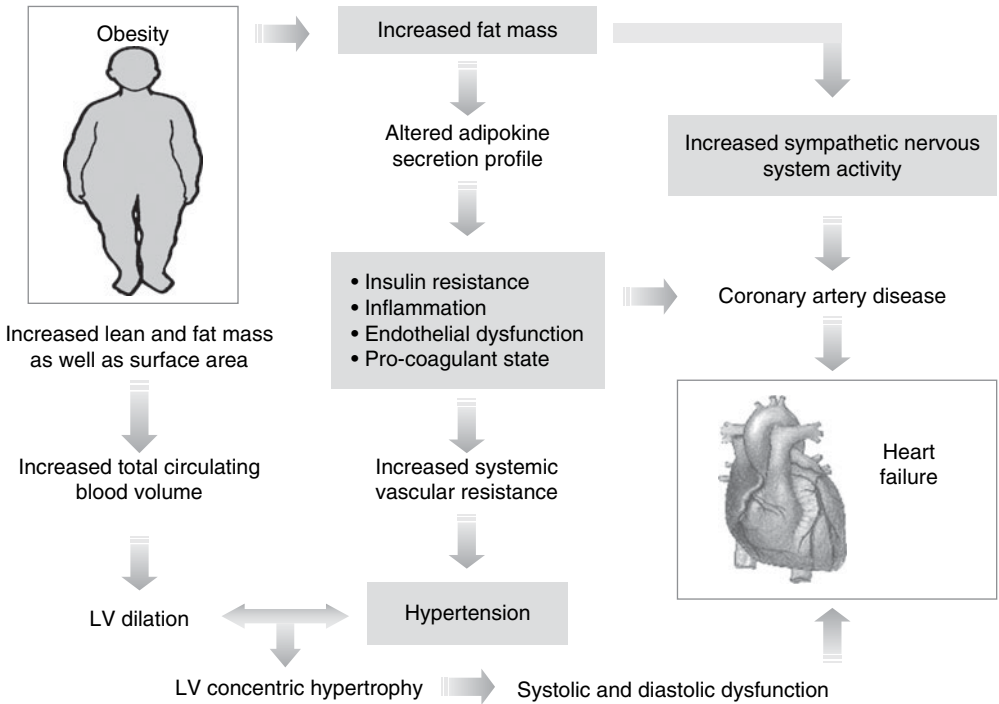


Fig. 9.1. Schematic diagram of obesity-associated cardiovascular alterations leading to heart failure.

concentric hypertrophy. In addition to increased blood pressure (BP) values, obese subjects exhibit an elevation of circulating concentrations of cardiovascular risk factors, which alters vascular function, adding further to the pressure load of the heart (Frühbeck, 2004). In spite of the increased cardiac output, obese individuals exhibit a decreased myocardial contractility proportional to excess body weight. LV hypertrophy, together with reduced ventricular compliance, results in diastolic dysfunction; a combination of systolic and diastolic dysfunction progresses to clinically significant risk of HF.

Adipokines and Cardiovascular Function

Adipose tissue acts as a metabolic active endocrine organ, secreting a large number of hormones, growth factors, enzymes, cytokines, complement factors and matrix proteins, collectively termed ‘adipokines’ (Frühbeck, 2004; Gualillo *et al.*, 2007). The physiological and pathophysiological relevance of adipokines in the homeostasis of the cardiovascular system resides in their effects on BP, fibrinolysis, angiogenesis, coagulation, vascular remodelling, insulin sensitivity and immunity, among others (Frühbeck, 2004; Wisse, 2004; Berg and Scherer, 2005;

Klein *et al.*, 2006; Sharma, 2006). In this respect, adipokines participate either directly or indirectly in the regulation of several processes that contribute to the development of inflammation, atherogenesis, hypertension and insulin resistance, as summarized in Table 9.1.

Table 9.1. Main adipokines implicated in cardiovascular homeostasis.

Adipokine	Cardiovascular effect	Reference
Adiponectin	Hormone with insulin-sensitizing, anti-inflammatory and anti-atherogenic properties	(Bodary and Eitzman, 2006)
Adipsin	Protein involved in the complement cascade	(Cianflone <i>et al.</i> , 2003)
Angiotensin II	Vasoconstrictor peptide that increases BP values and also participates in vascular remodelling	(Karlsson <i>et al.</i> , 1998)
Apelin	Vasoactive peptide that participates in the control of BP and stimulates cardiac contractility potently	(Tatemoto <i>et al.</i> , 1998)
ASP	Adipokine produced by the complement pathways that regulate whole-body glucose and lipid metabolism	(Cianflone <i>et al.</i> , 1989)
Cardiotrophin-1	Cytokine involved in the hypertrophy of cardiomyocytes	(Natal <i>et al.</i> , 2008)
Chemerin	Chemoattractant protein involved in adaptive and innate immunity	(Goralski <i>et al.</i> , 2007)
CRP	Acute-phase reactant involved in inflammatory processes	(Ouchi <i>et al.</i> , 2003a)
Ghrelin	Orexigenic hormone that exerts a depressor effect on BP and also exhibits cardioprotective properties	(Lin <i>et al.</i> , 2004)
IL-6	Proinflammatory cytokine implicated in inflammation and the acute-phase response	(Mohamed-Ali <i>et al.</i> , 1997)
Leptin	Anorexigenic hormone that participates in the inflammatory responses and contributes to the regulation of BP and other cardiovascular functions	(Frühbeck, 2004)
Osteopontin	Proinflammatory factor involved in vascular and myocardial remodelling	(Gómez-Ambrosi <i>et al.</i> , 2007)
PAI-1	Potent inhibitor of fibrinolysis that is implicated in atherosclerotic plaque formation	(De Taeye <i>et al.</i> , 2005)
RBP4	Protein apparently involved in the development of insulin resistance	(Quadro <i>et al.</i> , 1999)
Resistin	Hormone involved in insulin resistance also participating in the proinflammatory response	(Lehrke <i>et al.</i> , 2004)
SAA	Acute-phase reactant produced in response to injury, infection or inflammation	(Gómez-Ambrosi <i>et al.</i> , 2006)
TNF- α	Proinflammatory cytokine involved in systemic inflammation and the development of insulin resistance in obesity	(Moller, 2000)
Visfatin	Adipokine with apparent insulin-mimetic properties	(Fukuhara <i>et al.</i> , 2005)

Note: ASP, acylation-stimulating protein; BP, blood pressure; CRP, C-reactive protein; IL, interleukin; PAI-1, plasminogen activator inhibitor-1; RBP4, retinol-binding protein 4; SAA, serum amyloid A; TNF- α , tumour necrosis factor- α .

Inflammation and atherogenesis

Growing evidence highlights the relevant link between excess adiposity, inflammation and obesity-associated CVD. Adipose tissue constitutes an important source of circulating mediators of inflammation that participate in the mechanisms underlying vascular injury and atheromatous changes (Fig. 9.2). In addition to adipocytes, adipose tissue contains fibroblasts, preadipocytes, vascular constituents and, most importantly, macrophages. The resident macrophage population in adipose tissue ranges from 10% in lean humans to nearly 40% in obese subjects (Weisberg *et al.*, 2003). Macrophages are known to be crucial contributors to inflammation. However, adipocytes have also been recognized as key players in the chronic low-grade inflammation observed in obesity. In response to infectious and inflammatory signals, adipocytes synthesize and secrete several acute-phase reactants and mediators of inflammation, including

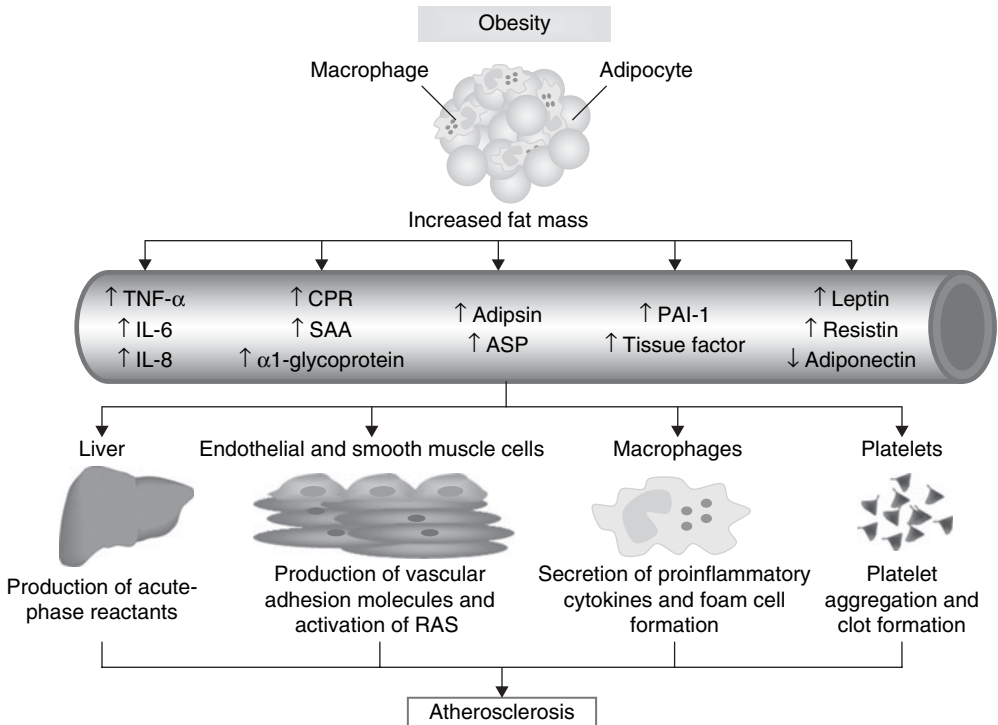


Fig. 9.2. Role of adipokines in the pathogenesis of atherosclerosis. Adipocytes and adipose tissue-embedded macrophages secrete proinflammatory cytokines, acute-phase reactants, complement factors, prothrombotic molecules and hormones implicated in the regulation of inflammation. The decrease of adiponectin secretion together with the excessive synthesis of the other prothrombotic, proinflammatory factors have been found to be associated with inflammation and vascular injury that leads to atherosclerotic plaque formation. RAS, renin–angiotensin system.

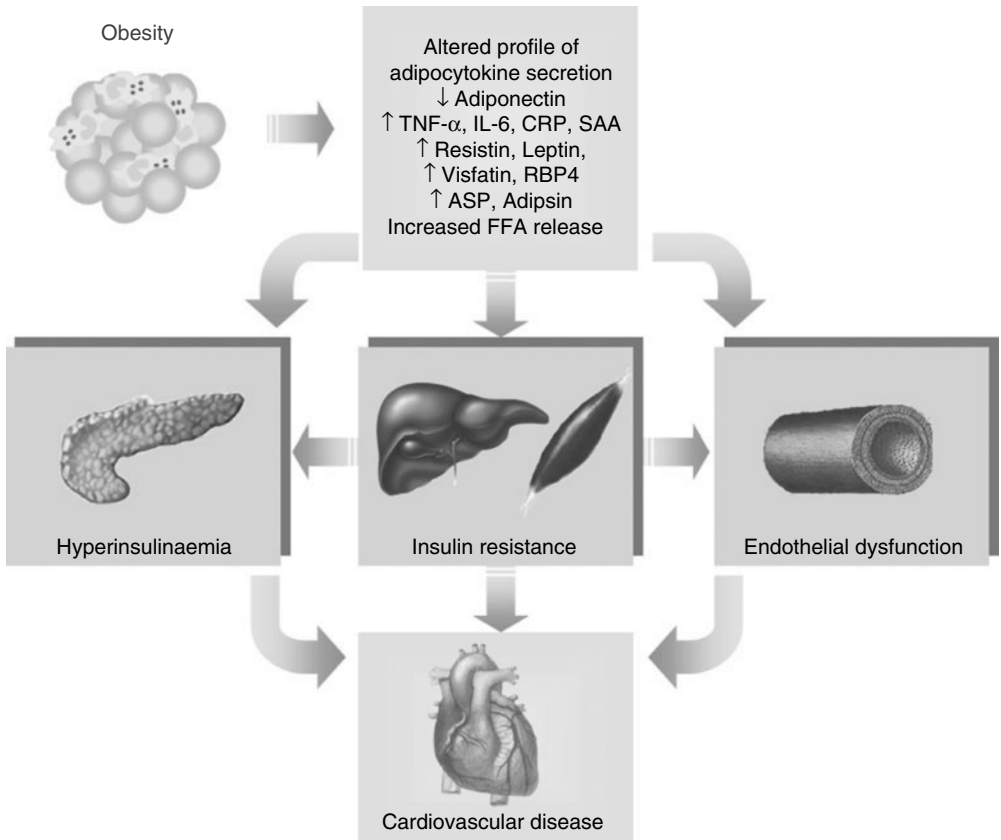


Fig. 9.3. Links between obesity-associated insulin resistance and cardiovascular disease. Excess free fatty acid (FFA) release in obesity overloads muscle, the liver and pancreatic β -cells. This ectopic lipid accumulation contributes to the development of insulin resistance, atherogenic dyslipidaemia and hyperinsulinaemia.

tumour necrosis factor- α (TNF- α), plasminogen activator inhibitor-1 (PAI-1), interleukin (IL)-1 β , IL-6, IL-8, IL-10 and IL-15, leukaemia inhibitory factor (LIF), serum amyloid A (SAA), complement factors B, D, C3 and prostaglandin E2, tissue factor and other inflammatory modulators such as adiponectin, leptin and resistin. These adipokines not only exert autocrine and paracrine effects, but are also secreted to the bloodstream, contributing to systemic inflammation that favours the acceleration of CVD development (Fig. 9.3).

Tumour necrosis factor- α

TNF- α is a proinflammatory cytokine that has been implicated in the pathogenesis of insulin resistance and obesity in both mice and humans (Hotamisligil *et al.*, 1995; Moller, 2000). Adipose tissue constitutes the main source of circulating

TNF- α since it is secreted primarily by the fat-embedded macrophages and, to a lesser extent, by adipocytes, highlighting the relevance of paracrine effects (Weisberg *et al.*, 2003). One of the mechanisms whereby TNF- α promotes insulin resistance constitutes the impairment of insulin signalling in adipocytes and skeletal muscle by interference with the insulin signalling cascade at early steps and, hence, impairment of insulin-stimulated glucose transport (Hotamisligil *et al.*, 1994; Hernández *et al.*, 2004). A second mechanism used by TNF- α to contribute to insulin resistance is through elevations in circulating free fatty acids (FFAs) caused by the stimulation of lipolysis and hepatic lipogenesis (Moller, 2000).

TNF- α is a well-known biomarker of systemic inflammation. Obesity and insulin resistance are correlated with increased circulating TNF- α concentrations (Hotamisligil *et al.*, 1995). Weight loss in obese subjects is accompanied by an improvement in insulin sensitivity and is also associated with a decrease in adipose tissue TNF- α mRNA expression. Moreover, circulating TNF- α has been shown to stimulate hepatic C-reactive protein (CRP) production, which, in turn, exerts an impact on the vasculature. TNF- α also exhibits a direct vascular effect through stimulation of the production of vascular adhesion molecules and cytokines in the endothelium and vascular wall, resulting in vascular inflammation, monocyte adhesion to the vessel wall and foam cell accumulation. The sustained expression of proinflammatory cytokines in both preclinical and clinical HF has prompted the study of their effects on LV function, remodelling and cardiomyopathy. The detrimental actions of TNF- α on LV dysfunction have been described as taking place within minutes, as well as after hours or days (Oral *et al.*, 1997). In this respect, elevated local TNF- α levels in the infarcted myocardium contribute to chronic LV dysfunction and acute myocardial rupture by inducing a marked local inflammatory response, matrix and collagen degradation, increased matrix metalloproteinase activity and apoptosis (Sun *et al.*, 2004).

Interleukin-6

Within adipose tissue, both adipocytes and macrophages secrete IL-6 and studies measuring arteriovenous increases of IL-6 levels have shown that adipose tissue accounts for approximately 30% of circulating IL-6 concentrations in humans (Mohamed-Ali *et al.*, 1997; Weisberg *et al.*, 2003). The production of IL-6 increases with increasing adiposity, with circulating IL-6 concentrations being highly correlated with the percentage of body fat. The proinflammatory role of IL-6 is based on the induction of the acute-phase reactant CRP in the liver, contributing to the chronic inflammatory state linked to obesity (Wisse, 2004). Although increased CRP production is the most recognized marker of IL-6, there are other IL-6-dependent factors that may contribute to the cardiovascular risk. IL-6 contributes to the risk of clot formation, enhancing the hepatic production of fibrinogen, another acute-phase reactant, as well as increasing both platelet number and activity (Burstein *et al.*, 1996; Esmon, 2004). Moreover, endothelial cells and vascular smooth muscle cells are targets of IL-6 action, resulting in an increased expression of adhesion molecules and activation of the local renin-angiotensin system, which favours vascular wall inflammation and damage (Wassmann *et al.*, 2004).

In a study performed in the Framingham population, a polymorphism in the IL-6 gene promoter (-174 G/C, G = major allele) has been reported to modify the association of obesity with the development of insulin resistance and the risk of T2DM (Herbert *et al.*, 2005, 2006). On the one hand, the -174 GG genotype is associated with lower plasma glucose concentrations being protective against the onset of T2DM (Herbert *et al.*, 2005). However, weight gain induces a higher degree of insulin resistance in men with a -174 IL-6 CC genotype (Herbert *et al.*, 2006). These studies underscore the importance of gene-environment interactions in T2DM. In this context, men with the -174 IL-6 CC genotype may benefit especially from weight loss regimens to improve the risk of developing T2DM.

Plasminogen activator inhibitor-1

PAI-1 is the most important inhibitor of fibrinolysis and it is synthesized by vascular tissues, platelets, liver and visceral adipose tissue (De Teye *et al.*, 2005). Elevations in plasma levels of PAI-1 are characteristic of obesity and contribute to the increased risk of atherothrombotic events in excess body weight and the metabolic syndrome (Sobel, 1999; Mertens *et al.*, 2006). Increased plasma PAI-1 concentrations are derived directly from cellular constituents of fat (adipocytes, stroma-vascular or adipose tissue matrix cells) or indirectly through the effects of other adipose-derived factors (TNF- α , Ang II, TGF- β , FFA) that stimulate local and systemic PAI-1 production (Fain *et al.*, 2004; De Teye *et al.*, 2005). Obesity is also associated with increased circulating concentrations of the procoagulants fibrinogen, von Willebrand factor, factor VII and tissue factor. Many of the circulating cytokines elevated in obesity trigger an endothelial activation, which results in platelet aggregation and clot formation (Davi *et al.*, 2002; Gómez-Ambrosi *et al.*, 2002). Thus, the increase in clotting factor levels, together with platelet activation, constitute a procoagulant state, which contributes to atherogenesis via the deposition of platelets and fibrinous products in the developing plaques.

Adiponectin

Adiponectin (also known as Acrp30, AdipoQ, apM1 and gelatin-binding protein 28) is synthesized mainly by adipocytes and can be found in three oligomeric forms; namely as trimer, hexamer and high molecular weight molecules (Maeda *et al.*, 1996; Waki *et al.*, 2003). Adiponectin displays anti-diabetic and anti-atherogenic properties and is reduced in patients with obesity, T2DM and CAD (Arita *et al.*, 1999; Ouchi *et al.*, 1999; Hotta *et al.*, 2000). Two adiponectin receptors (AdipoR1 and AdipoR2) have been described (Yamauchi *et al.*, 2003). AdipoR1 is widely expressed in muscle, whereas AdipoR2 is expressed mainly in the liver. These receptors mediate the insulin-sensitizing action of adiponectin by increasing the activity of AMP kinase and peroxisome proliferator-activated receptor- α (PPAR α) ligands, as well as fatty oxidation and glucose uptake. Adiponectin-deficient mice develop diet-induced insulin resistance on a high-fat, high-sucrose diet (Maeda *et al.*, 2002), while sustained peripheral expression of adiponectin decreases the development of diet-induced obesity and improves insulin sensitivity (Shklyaev *et al.*, 2003). Clinically, elevated adiponectin concentrations have been shown to be associated with higher insulin sensitivity and

a reduced risk of T2DM (Hotta *et al.*, 2000, 2001; Spranger *et al.*, 2003). Thus, the development of interventions that increase adiponectin levels has been proposed as a target to improve insulin sensitivity and glucose tolerance, and probably coronary heart disease (CHD) (Bodary and Eitzman, 2006).

Adiponectin exerts an anti-inflammatory effect by downregulating the expression of adhesion molecules in endothelial cells, upregulating anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist in monocytes and suppressing lipid accumulation and interferon- γ (IFN- γ) in macrophages. Most of the anti-inflammatory properties of adiponectin in endothelial cells and macrophages are mediated by the inhibition of the nuclear factor- κ B (NF- κ B) pathway. Likewise, adiponectin plays a protective role against atherosclerotic vascular alterations. Exogenous administration of adiponectin protects apolipoprotein E-deficient mice against the development of atherosclerosis. Adiponectin reduces the proliferation and migration of vascular smooth muscle cells by decreasing the effects of growth factors, such as platelet-derived growth factor (PDGF) and heparin-binding epidermal growth factor (HBEGF). In this regard, adiponectin-deficient mice exhibit an exaggerated vascular remodelling response to injury and an impaired endothelium-dependent vasodilation on an atherogenic diet (Ouchi *et al.*, 2003b), increased leukocyte-endothelium adhesiveness (Ouedraogo *et al.*, 2007), increased neointimal hyperplasia after acute vascular injury (Kubota *et al.*, 2002; Matsuda *et al.*, 2002) and increased BP values compared with their wild-type littermates (Ohashi *et al.*, 2006). The beneficial effects of adiponectin on the endothelium are mediated by its ability to increase nitric oxide (NO) bioavailability (Li *et al.*, 2007).

In humans, hypoadiponectinaemia has been linked to endothelial dysfunction, CAD and stroke, with concentric hypertrophy and diastolic dysfunction commonly being observed in diabetes and other obesity-related disorders which are associated with decreased adiponectin concentrations (Kumada *et al.*, 2003; Shimabukuro *et al.*, 2003; Shibata *et al.*, 2004; Chen *et al.*, 2005). The local production of adiponectin by cardiomyocytes suggests an autocrine-paracrine effect (Piñeiro *et al.*, 2005). Adiponectin exerts its cardioprotective role modulating myocardial remodelling after ischaemic injury through AMPK and cyclo-oxygenase-2 (COX-2) (Ishikawa *et al.*, 2003; Shibata *et al.*, 2005), attenuating cardiac hypertrophy and interstitial fibrosis (Shibata *et al.*, 2004, 2007). Accordingly, high plasma adiponectin concentrations are associated with lower risk of acute coronary syndrome (Wolk *et al.*, 2007), infarction in men (Pischon *et al.*, 2004) and CHD in diabetic patients (Schulze *et al.*, 2005). However, other studies have found hyperadiponectinaemia in patients with chronic and congestive HF (Kistorp *et al.*, 2005; George *et al.*, 2006). Furthermore, a meta-analysis has reported that any association of adiponectin with CHD risk is comparatively moderate and requires further investigation (Sattar *et al.*, 2006).

Serum amyloid A

SAA is the major acute-reactant protein produced in the liver in response to infection, inflammation, injury and stress (Jensen and Whitehead, 1998; Uhlir

and Whitehead, 1999). It has been reported that SAA can be more sensitive than CRP as an indicator of inflammation in some non-cardiovascular inflammatory conditions (Malle and De Beer, 1996). SAA is an apolipoprotein and a component of high-density lipoprotein (HDL) particles (Jensen and Whitehead, 1998). Increased concentrations of SAA are associated with an elevated risk of CVD (Morrow *et al.*, 2000; Jousilahti *et al.*, 2001; Delanghe *et al.*, 2002). During the non-acute-phase reaction, adipose tissue constitutes the major expression site of SAA, providing a direct link between adipose tissue mass and cardiovascular risk (Sjöholm *et al.*, 2005).

Adipocyte-derived SAA stimulates lipolysis in an autocrine way and, consequently, induces an increase in the release of FFA and a decrease in insulin sensitivity (Yang *et al.*, 2006). SAA also acts as a paracrine factor stimulating the secretion of proinflammatory cytokines (IL-6, IL-8, MCP-1) in adipose stromal-vascular cells. In addition, macrophages infiltrated in the adipose tissue may also constitute target cells for SAA action, further increasing the release of cytokines and chemokines. Finally, circulating SAA also stimulates the release of inflammatory cytokines from endothelial cells and monocytes, contributing to the infiltration of monocytes into the vasculature and to endothelial dysfunction, thus accelerating the development of atherosclerosis. In addition, the interaction of SAA with HDL further aggravates the atherosclerotic process, since SAA is incorporated into HDL particles and impairs its function. Taken together, SAA is a direct mediator of obesity-associated inflammation and its related cardio-metabolic consequences. Importantly, weight loss reduces circulating SAA concentrations, which may mediate, in part, the improvements in systemic inflammation and cardiovascular risk associated with weight reduction (Gómez-Ambrosi *et al.*, 2006). Thus, SAA may be a valuable diagnostic and prognostic marker of obesity-associated CVD.

C-reactive protein

Circulating C-reactive protein (CRP) concentrations are strongly associated with obesity and obesity-related diseases, including insulin resistance, T2DM and hyperlipidaemia (Ouchi *et al.*, 2003a; Flórez *et al.*, 2006). In fact, obesity is the major determinant of elevated CRP levels in subjects with the metabolic syndrome (Aronson *et al.*, 2004). CRP is an acute-phase reactant produced by the liver and a well-known marker of chronic low-grade inflammation. It is a member of the pentraxin family that attaches damaged cells causing cell death through the activation of the complement cascade (Pepys and Hirschfield, 2003). Excess adiposity drives to an enhanced production of proinflammatory cytokines such as IL-6 and TNF- α , which, in turn, stimulate the hepatic production of CRP (Flórez *et al.*, 2006). Moreover, human adipose tissue reportedly produces CRP and an inverse relationship between CRP and adiponectin in both plasma and adipose tissue has been observed (Ouchi *et al.*, 2003a). Modest elevations in CRP are associated with the pathogenesis of atherosclerosis, with increased CRP concentrations being a risk factor for CHD. Thus, the measurement of CRP is recommended in some clinical settings to stratify CVD risk and to guide clinical management (Pearson *et al.*, 2003).

Osteopontin

Osteopontin, also known as early T-lymphocyte activation, secreted phosphoprotein-1 and bone sialoprotein-1, is a phosphoprotein identified originally in osteoblasts and osteoclasts that has been shown subsequently to be secreted by a wide variety of cells (Naldini *et al.*, 2006; Rangaswami *et al.*, 2006), including adipocytes (Gómez-Ambrosi *et al.*, 2007). Although associated initially with bone mineralization, it has been recognized that osteopontin also participates in wound healing and inflammation, as well as immunity. Osteopontin influences cardiovascular function, playing a role in atherosclerosis (Isoda *et al.*, 2003), LV hypertrophy (Graf *et al.*, 1997) and cardiac fibrosis (Lenga *et al.*, 2008), processes commonly associated with obesity. In this regard, circulating osteopontin levels reportedly are increased in obesity (Gómez-Ambrosi *et al.*, 2007). Interestingly, in the post-infarcted heart, osteopontin has been shown to operate coordinating the intracellular signals required to integrate myofibroblast proliferation, migration and extracellular matrix deposition with the recruitment of macrophages and initiation of collateral vessel formation, thus ensuring that the mechanical properties of the heart are not further compromised (Zahradka, 2008).

Hypertension

Obesity, in particular if accompanied by an increased visceral fat accumulation, is an independent risk factor for the development of hypertension. A prospective study performed in the Framingham population showed that overweight and obesity are associated with an increased relative risk for the onset of hypertension (Wilson *et al.*, 2002). It is well documented that BP increases with weight gain and decreases with weight loss. Alterations in sodium and water reabsorption have been shown to participate in the onset of obesity-associated hypertension (Krauss *et al.*, 1998). An increased arterial pressure is required to maintain sodium balance in obese subjects, indicating an impaired renal natriuresis (Hall, 1997). Both glomerular filtration rate and renal plasma flow are elevated in obesity, suggesting that impaired renal excretion is a consequence of increased renal tubular reabsorption. In addition, the stimulation of the sympathetic nervous system (SNS) found in obesity further worsens the renal tubular reabsorption and altered natriuresis (Esler, 2000).

Obesity-associated hypertension results from the complex interaction between haemodynamic and endocrine-metabolic factors. Among the latter, a central role has been attributed to insulin resistance, which characterizes both obesity and hypertension (Krauss *et al.*, 1998). In the past decade, growing evidence supports the contribution of adipose tissue-derived factors in BP homeostasis, thus improving our understanding of obesity-related hypertension.

Leptin

Leptin, the *OB* gene product, participates in the control of body weight by regulating food intake and energy expenditure (Frühbeck *et al.*, 2001). Leptin secretion is proportional to the amount of adipose tissue stores, with plasma concentrations

being increased markedly in obese individuals (Considine *et al.*, 1996). Beyond its participation in the maintenance of energy balance, leptin contributes to the homeostasis of the vascular tone (Frühbeck, 2004). It is suggested that hyperleptinaemia plays an important role in the pathogenesis of obesity-associated hypertension (Agata *et al.*, 1997; Ren, 2004; Rahmouni *et al.*, 2005). Intracerebroventricular and intravenous administration of leptin reportedly increases mean arterial pressure (MAP) and HR, as well as sympathetic outflow to kidneys, adipose tissue, skeletal vasculature and adrenal medulla in rodents (Matsumura *et al.*, 2000). Leptin increases the vasomotor sympathetic activity through the activation of leptin receptors (OB-R) in the ventromedial and dorsomedial hypothalamic regions (Haynes *et al.*, 1997; Marsh *et al.*, 2003). Interestingly, administration of leptin is not always accompanied by changes in MAP and HR (Haynes *et al.*, 1997; Shek *et al.*, 1998; Frühbeck, 1999). The explanation for this apparent paradox is that, in addition to its central sympathoexcitatory action, leptin induces a depressor effect simultaneously in peripheral tissues. Leptin also has been shown to induce a depressor response attributable to the vasodilation of conduit and resistance vessels (Frühbeck, 1999; Lembo *et al.*, 2000; Beltowski *et al.*, 2006). In the aorta and coronary arteries, leptin reportedly induces vasodilation via NO (Kimura *et al.*, 2000; Lembo *et al.*, 2000; Knudson *et al.*, 2005), whereas the relaxation induced by the hormone in mesenteric arteries is mediated by the endothelium-derived hyperpolarizing factor (EDHF) (Lembo *et al.*, 2000; Gálvez *et al.*, 2006). Leptin also inhibits the Ang II-induced calcium increase and vasoconstriction in the smooth muscle layer of the aorta (Fortuño *et al.*, 2002; Rodríguez *et al.*, 2007b). A further mechanism whereby leptin decreases BP values is the induction of natriuresis and diuresis at the tubular level through NO-dependent mechanisms (Jackson and Li, 1997; Villarreal *et al.*, 1998, 2004). Finally, leptin reduces insulin secretion and improves insulin sensitivity in skeletal muscle and the liver (Zhao *et al.*, 1998, 2000; Yaspelkis *et al.*, 2001). Leptin, therefore, appears to have a dual effect on BP control with a pressor response attributable to sympathetic activation via the central nervous system and a depressor response attributable to a direct effect of leptin on peripheral tissues (Fig. 9.4).

Leptin has been found to be synthesized by cardiomyocytes and released to the coronary effluent, raising the possibility that cardiac leptin exerts direct physiological effects on the myocardium (Purdham *et al.*, 2004). In this sense, leptin has been shown to decrease the contractility of ventricular myocytes via NO (Nickola *et al.*, 2000) and to promote the hypertrophy of rat cardiomyocytes via activation of the mitogen-activated protein kinase cascade (Rajapurohitam *et al.*, 2006). Moreover, leptin exhibits a cardioprotective effect in myocardial ischaemia-reperfusion injury (Smith *et al.*, 2006). After a brief period of myocardial ischaemia, a rapid local inflammatory cascade takes place in the infarcted tissue after reperfusion. Since inflammation and vascularization play an important role in tissue healing, the proinflammatory properties, together with the angiogenic and wound-healing actions of leptin, may improve the infarcted tissue repair considerably (Bouloumié *et al.*, 1998; Otero *et al.*, 2005). Taken together, the local production of leptin and the presence of OB-R in cardiac myocytes indicate that this cytokine acts as an autocrine and paracrine agent in cardiac function regulation under both physiological and pathophysiological conditions.

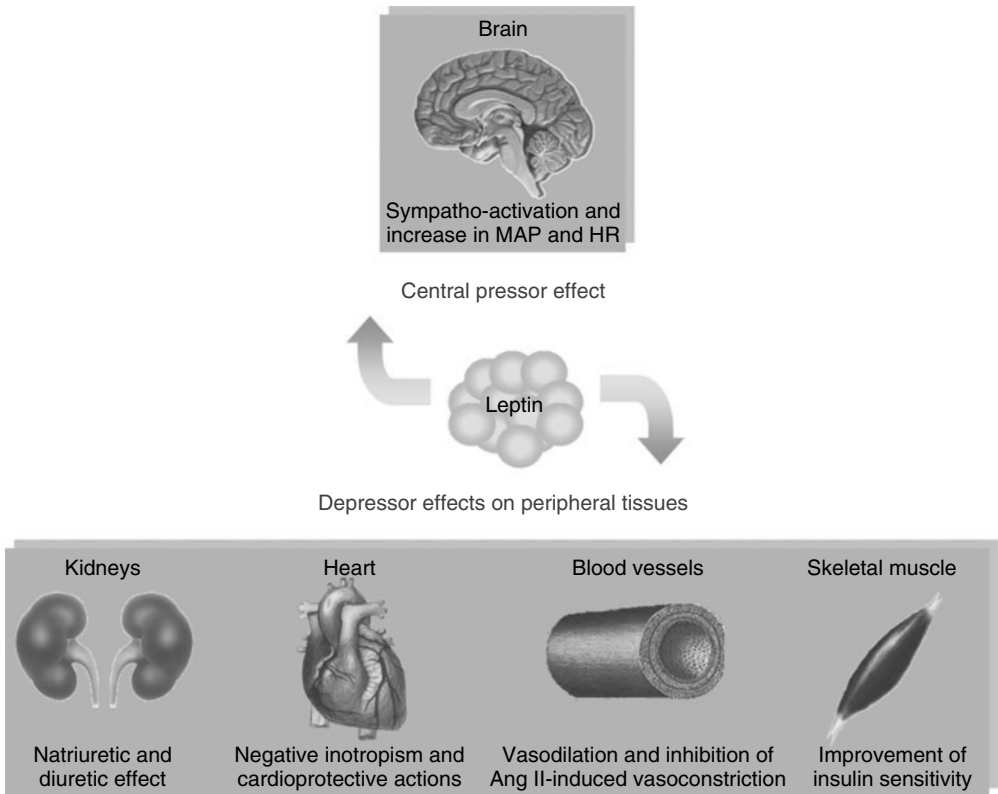


Fig. 9.4. Dual effects of leptin on blood pressure control. MAP, mean arterial pressure; HR, heart rate; Ang II, angiotensin II.

Leptin predicts the worsening of features of the metabolic syndrome independently of obesity (Franks *et al.*, 2005). Leptin levels are elevated in essential hypertension, suggesting a possible link between hyperleptinaemia and cardiovascular dysfunction in hypertension (Agata *et al.*, 1997). In this respect, it has been reported that the beneficial vascular, renal and cardiac responses induced by leptin are impaired in hypertensive rats (Villarreal *et al.*, 1998; Wold *et al.*, 2002; Gálvez *et al.*, 2006; Rodríguez *et al.*, 2006). Moreover, a strong positive correlation was found between hyperleptinaemia and tachycardia in mildly obese and mildly hypertensive patients (Narkiewicz *et al.*, 1999). Furthermore, hyperleptinaemia constitutes an independent risk marker for different cardiovascular events, such as chronic heart failure (CHF) or ischaemic and non-ischaemic stroke, indicating that leptin represents an important link between obesity and CVD (Schulze *et al.*, 2003; Söderberg *et al.*, 2003). Nevertheless, it has to be taken into consideration that the supposedly detrimental effects of leptin on cardiovascular homeostasis may only underlie a state of leptin-resistance, which has been shown clearly in obese subjects (Caro *et al.*, 1996; Rahmouni *et al.*, 2005).

Ghrelin

Ghrelin is a growth hormone (GH)-releasing peptide, isolated originally from the stomach, identified as an endogenous ligand for the GH secretagogue receptor (GHS-R) (Kojima *et al.*, 1999). Although gastric and intestinal ghrelin constitute the two major origins of this hormone (Kojima *et al.*, 1999), ghrelin is also synthesized to a lesser extent by adipose tissue (Knerr *et al.*, 2006). Two major forms of ghrelin are present in plasma and stomach: ghrelin, with an *n*-octanoyl group at the serine 3 residue, and desacyl-ghrelin, without the acylation (Hosoda *et al.*, 2000). Ghrelin acts on the pituitary and hypothalamus to stimulate GH release, food intake and weight gain (Tschöp *et al.*, 2000, 2001; Wren *et al.*, 2000, 2001; Wortley *et al.*, 2004; Ahima, 2006). The secretion of GH stimulated by ghrelin is independent of that evoked by the hypothalamic GH-releasing hormone (GHRH). GH and its mediator, insulin-like growth factor (IGF)-1, are anabolic hormones that are essential for myocardial development and performance. Ghrelin has cardiovascular effects through both GH-dependent and -independent mechanisms (Fig. 9.5).

Ghrelin acts on the neurones of the nucleus tractus solitarius to decrease MAP in rodents (Lin *et al.*, 2004; Tsubota *et al.*, 2005). Intravenous administration of ghrelin to healthy individuals and patients with CHF decreases MAP without changing HR and improves cardiac function by increasing stroke volume and the cardiac index (Nagaya *et al.*, 2001a,b). The beneficial haemodynamic effects of ghrelin in patients with CHF seem to be attributable to both an inotropism of GH and a fall in cardiac overload. The presence of GHS-R in cardiac ventricles provides evidence for direct cardiac effects of ghrelin (Iglesias *et al.*, 2004), which has been shown to be synthesized by cardiomyocytes and to operate as an endogenous cardioprotective factor protecting cardiomyocytes and endothelial cells against apoptosis through the activation of an intracellular survival pathway (Baldanzi *et al.*, 2002). Moreover, ghrelin administration after myocardial infarction has been shown to attenuate LV enlargement and myocardial fibrosis in rodents (Soeki *et al.*, 2008).

Based on the widespread expression of ghrelin and GHS-R in the human cardiovascular system, the possible participation of ghrelin in the paracrine regulation of the vascular tone was investigated further (Kleinz *et al.*, 2006). Intra-arterial infusion of ghrelin to healthy individuals induces vasodilation through GH/IGF-1-independent mechanisms (Okumura *et al.*, 2002). Moreover, ghrelin improves the endothelial dysfunction of patients with the metabolic syndrome by increasing NO bioavailability (Tesauro *et al.*, 2005). In addition, both ghrelin and desacyl-ghrelin potently reverse endothelin-1-induced vasoconstriction, a peptide that is upregulated in atherosclerosis (Kleinz *et al.*, 2006). In this sense, ghrelin may play a modulatory role in atherosclerosis since this peptide also inhibits proinflammatory cytokine production, mononuclear cell binding and NF- κ B activation in human endothelial cells *in vitro* and endotoxin-induced cytokine production *in vivo* (Li *et al.*, 2004). In summary, the low circulating ghrelin concentrations found in obese and hypertensive patients might be haemodynamically disadvantageous, due to the positive vascular and anti-inflammatory properties of ghrelin (Tschöp *et al.*, 2001; Yildiz *et al.*, 2004; Poynko *et al.*, 2005).

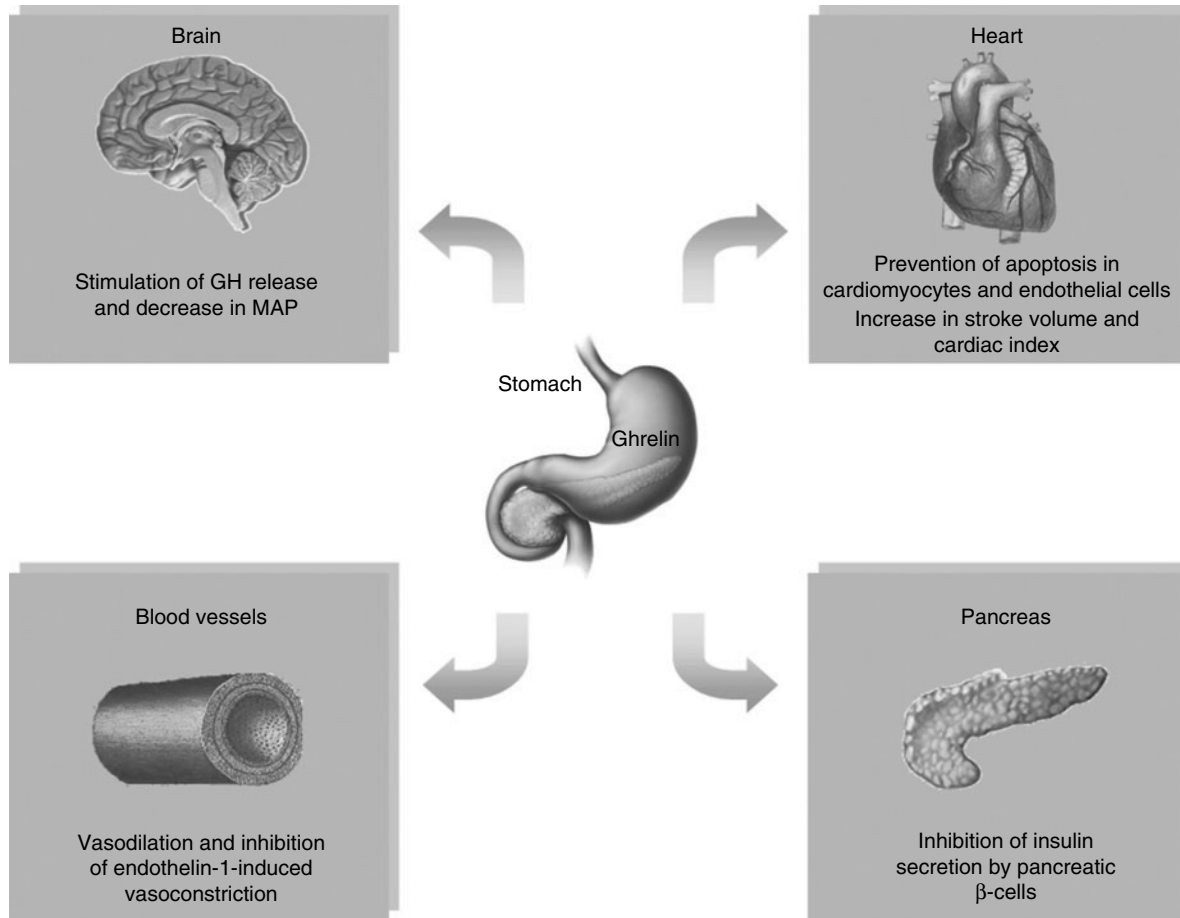


Fig. 9.5. Participation of ghrelin in cardiovascular homeostasis. GH, growth hormone; MAP, mean arterial pressure.

Angiotensinogen–Angiotensin II

Angiotensin (Ang) II is a well-known hypertensive hormone, derived from the precursor molecule angiotensinogen, which is cleaved by enzymes of the renin–angiotensin system (RAS) [renin, angiotensin-converting enzyme (ACE)], as well as the non-renin-angiotensin system (NRAS) (cathepsin D, cathepsin G, tonin, chymase) (Karlsson *et al.*, 1998). Human adipose tissue has been shown to express angiotensinogen and the enzymes required for its conversion to Ang II. Likewise, both Ang II receptor subtypes, AT₁ and AT₂, are expressed in the cell membrane of adipocytes (Crandall *et al.*, 1994). Obese individuals reportedly exhibit elevated circulating concentrations of ACE, angiotensinogen, renin and aldosterone and increased adipose tissue angiotensinogen expression (Engeli *et al.*, 2005). A 5% reduction in body weight leads to a meaningful reduction in the renin–angiotensin–aldosterone system in plasma and adipose tissue, contributing to systolic BP decrease. Collectively, these findings show that adipose tissue constitutes an important peripheral site of Ang II production and a target for this hypertensive hormone, suggesting the involvement of adipocyte-derived Ang II in obesity-associated hypertension (Kim and Moustaid-Moussa, 2000).

Apelin

Apelin was identified as the endogenous ligand of an orphan G protein-coupled receptor, the human APJ receptor (Tatemoto *et al.*, 1998). To date, four forms of the peptide have been isolated (apelin-12, 13, 17 and 36), each showing different receptor-binding capabilities. Similarities between the structure and anatomical distribution of apelin and its receptor and that of Ang II and the AT₁ receptor provide clues about its potential cardiovascular effects (Lee *et al.*, 2006). Apelin is expressed in rat and human adipocytes and is influenced markedly by the nutritional status, with its expression being reduced during fasting and increased by re-feeding (Boucher *et al.*, 2005). Insulin also influences the production of apelin in adipose tissue, upregulating its synthesis both *in vitro* and *in vivo*.

The cardiovascular system appears to be a primary target of apelin since APJ is expressed in the heart and the media layer of human coronary arteries, aorta and saphenous vein grafts. The intravenous administration of apelin to rats is followed by a decrease in MAP through NO-dependent mechanisms ranging from 5% for apelin-36 to 25% for apelin-12 (Tatemoto *et al.*, 2001). This hypotensive effect is accompanied by a slight increase in HR, which results from the baroreceptor reflex-mediated stimulation of the SNS. In this sense, it has been reported that apelin increases myocardial contractility in isolated perfused rat hearts (Szokodi *et al.*, 2002). Moreover, circulating apelin concentrations, atrial apelin and atrial and ventricular APJ expression are decreased markedly in patients with HF (Földes *et al.*, 2003). It has been reported recently that in ischaemic myocardium of isolated rat heart, apelin expression is upregulated but returns back to baseline values after reperfusion (Kleinz and Baxter, 2008). During the period of reduced apelin expression, administration of exogenous apelin-13 attenuated the ischaemic/reperfusion injury, reducing the infarct size.

In spite of increasing myocardial contractility (Szokodi *et al.*, 2002), apelin exerts a weak effect on cardiac output, probably because it induces vasodilation

and reduces the preload. Apelin-12 has been shown to dilate peripheral veins more efficiently than the Ca^{2+} -antagonists, hydralazine or nitroglycerin (Cheng *et al.*, 2003). This hypotensive effect is accompanied by a slight increase in HR, which results from the baroreceptor reflex-mediated stimulation of the SNS. Moreover, APJ-deficient mice have been shown to increase the vasopressor response to the potent vasoconstrictor Ang II, suggesting that APJ might play a counter-regulatory role opposing the pressor action of Ang II (Ishida *et al.*, 2004). The evidence that apelin acts as a vasodilator as well as a cardioprotective factor and that the sensitivity to apelin might be altered in disease states makes the apelin-APJ system a promising therapeutic target.

Insulin resistance and type 2 diabetes mellitus

Insulin resistance is one of the core defects of the metabolic syndrome, lying at the centre of the pathogenesis of T2DM and the associated CVD risk. As mentioned before, the proinflammatory mediators released by adipose tissue (PAI-1, TNF- α , IL-6, resistin and others), together with hyposecretion of beneficial adipokines (such as adiponectin), exert a detrimental effect on vascular endothelial function, thereby increasing the CVD risk in the metabolic syndrome.

Resistin

Resistin, also known as Fizz3, is a member of a gene family that includes resistin-like molecule α (RELM- α), RELM- β and RELM- γ . In mice, resistin is produced mainly by adipocytes (Yang *et al.*, 2003). In humans, resistin is strongly expressed by macrophages and, in lesser amounts, by fat cells. According to its name, resistin was found to increase insulin resistance in obese mice (Steppan *et al.*, 2001). Moreover, treatment of a murine adipocyte cell line with thiazolidinedione (TZD), an anti-diabetic drug that increases insulin sensitivity via the stimulation of PPAR γ , decreases resistin expression markedly in adipocytes. Despite the clear link between elevated serum resistin concentrations in obese mice, the association between circulating resistin levels and obesity in humans is more controversial. Several groups have described increased concentrations of resistin in human obesity (Azuma *et al.*, 2003; Degawa-Yamauchi *et al.*, 2003), while others report no differences (Lee *et al.*, 2003; Silha *et al.*, 2003; Heilbronn *et al.*, 2004). Studies of the association of plasma resistin levels with insulin resistance and T2DM have also yielded inconsistent results. In spite of the hyperresistinaemia found in diabetic animal models, several human studies reported no differences in circulating concentrations of resistin among normal subjects and patients with insulin resistance or T2DM (Lee *et al.*, 2003; Silha *et al.*, 2003; Heilbronn *et al.*, 2004; Iqbal *et al.*, 2005; Kusminski *et al.*, 2005), while some authors reported that subjects with T2DM exhibited higher resistin levels (McTernan *et al.*, 2003; Youn *et al.*, 2004). In addition, whereas murine models of insulin resistance show dramatic changes in resistin expression after treatment with PPAR γ agonists, such agents have more modest effects in humans (Savage *et al.*, 2001). Taken together, the relation between obesity, adipose tissue resistin expression, systemic insulin

resistance and amelioration of the latter by PPAR γ agonists reported in mice may not translate completely to human pathophysiology.

Growing evidence links resistin with inflammation and CVD (Lehrke *et al.*, 2004; Gómez-Ambrosi and Frühbeck, 2005; Yaturu *et al.*, 2006). A significant association between hyperresistinaemia and proatherogenic inflammatory markers, unstable angina, congestive HF and coronary atherosclerosis has been shown (Gómez-Ambrosi and Frühbeck, 2001; Reilly *et al.*, 2005; Kunnari *et al.*, 2006; Lubos *et al.*, 2007; Norata *et al.*, 2007; Takeishi *et al.*, 2007). Macrophages infiltrating human atherosclerotic aneurysms have been shown to secrete resistin (Jung *et al.*, 2006). In turn, resistin stimulates the synthesis of proinflammatory cytokines such as TNF- α , IL-1, IL-6 and IL-12 through an NF- κ B dependent pathway, upregulates the expression of adhesion molecules (VCAM1 and ICAM1) and promotes the release of endothelin-1 in the human endothelial cells (Tilg and Moschen, 2006). Interestingly, resistin also stimulates the synthesis of monocyte chemoattractant protein-1 (MCP-1) in the endothelium, which might perpetuate a vicious circle of macrophage recruitment and production of proinflammatory cytokines (Verma *et al.*, 2003). Furthermore, resistin induces endothelial dysfunction in isolated coronary artery rings (Dick *et al.*, 2006) and worsens cardiac ischaemia-reperfusion injury in isolated perfused rat hearts (Rothwell *et al.*, 2006). In this respect, patients with CAD exhibit a strong correlation between resistin levels and inflammatory markers, namely CRP and TNF- α (Yaturu *et al.*, 2006). Recently, resistin has been shown to be able to induce a selective vascular insulin resistance-impairing endothelial IRS-1 signalling pathway that leads to endothelial nitric oxide synthase (eNOS) activation and vasodilation (Gentile *et al.*, 2008). Although a clear-cut function for resistin in humans is still lacking, it may play a role in the progression from vascular inflammation to endothelial dysfunction and accelerate the eventual development of overt CVD (Gómez-Ambrosi and Frühbeck, 2005).

Visfatin

Visfatin, which was identified initially as pre-B-cell-colony-enhancing factor, is produced mainly by visceral adipose tissue of mice and humans (Fukuhara *et al.*, 2005). Acute and chronic administration of visfatin to mice reduces glycaemia without changes in insulin concentrations. Visfatin apparently was reported to bind to the insulin receptor at a different site from insulin to exert insulin-mimetic properties, such as the stimulation of glucose uptake and lipogenesis in 3T3-L1 adipocytes or L6 myocytes, and the suppression of glucose production by cultured hepatocytes (Fukuhara *et al.*, 2005). In addition, visfatin facilitates adipogenesis by stimulating markers of adipocyte differentiation, including PPAR γ , fatty acid synthase, diacylglycerol acyltransferase or adiponectin (Fukuhara *et al.*, 2005). However, part of these findings are currently controversial, with the authors having been forced to retract some of their original conclusions (Fukuhara *et al.*, 2007).

To date, the relationship between visfatin, obesity and T2DM remains controversial. Increased plasma visfatin concentrations have been reported in patients with type 2 diabetes, gestational diabetes and obesity (Fukuhara *et al.*,

2005; Chen *et al.*, 2006; Krzyzanowska *et al.*, 2006), while other studies have found reduced visfatin levels in obesity and no correlation with insulin resistance (Pagano *et al.*, 2006). Interestingly, hyperglycaemia causes an increase in circulating visfatin concentrations, with this increase being more prominent as glucose intolerance worsens in patients with T2DM (Dogru *et al.*, 2007). Improvement of the glycaemic profile with either exercise training or weight loss lowers the elevated visfatin levels found in patients with obesity and type 1 diabetes mellitus (Haider *et al.*, 2006a,b). Thus, the increase in visfatin synthesis associated with obesity and diabetes may represent a compensatory mechanism to maintain normoglycaemia. In fact, TZD treatment in healthy volunteers increases the release of visfatin from adipose tissue, improving their insulin sensitivity, with FFA reportedly counteracting this effect. Recently, it has been observed that visfatin upregulates key molecules of the angiogenic process, such as matrix metalloproteinases (MMP) and vascular endothelial growth factor (VEGF) in human endothelial cells (Adya *et al.*, 2008), revealing a novel insight into the potential role of visfatin in CVD.

Retinol-binding protein 4

Retinol-binding protein 4 (RBP4) is the only specific transport protein for retinol (vitamin A) and its main function is to deliver retinol to tissues (Quadro *et al.*, 1999). Recently, it has been shown that this adipokine may contribute to the pathogenesis of T2DM. Transgenic overexpression of human RBP4 or injection of RBP4 to normal mice causes insulin resistance, whereas genetic deletion of *Rbp4* enhances insulin sensitivity (Yang *et al.*, 2005). Circulating RBP4 is increased substantially, not only in several murine models of obesity and insulin resistance but also in humans with these conditions (Yang *et al.*, 2005; Graham *et al.*, 2006). It has been proposed that adipocytes might detect the absence of glucose uptake by the glucose transporter, GLUT4, and in response, secrete adipokines such as RBP4 to restrict glucose uptake by skeletal muscle and increase hepatic glucose output via the induction of the expression of the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEPCK), thereby increasing glycaemia (Tamori *et al.*, 2006). However, in human obesity, the exact contribution of RBP4 has not been disentangled completely, with some studies observing normal concentrations in obese, insulin-resistant and also diabetic patients (Janke *et al.*, 2006; Broch *et al.*, 2007; Gómez-Ambrosi *et al.*, 2008). Further research is needed to unravel the involvement of RBP4 in the development of obesity-associated insulin resistance in humans.

Acylation-stimulating protein: C3, factor B and adipsin

Acylation-stimulating protein (ASP) was determined initially in human plasma and identified as a derivative of the third complement component (C3) (Cianflone *et al.*, 1989). ASP is a hormone produced by adipocytes through the interaction of C3 with factor B and adipsin in the alternative complement pathway; none the less, ASP potentially could be generated through the two other complement pathways, the classical and the lectin pathway (Cianflone *et al.*, 2003). ASP increases the esterification of FFA into triacylglycerol (TG) synthesis in

fat-storing cells. This effect is achieved through the stimulation of glucose uptake (by enhancing the translocation of glucose transporters to the plasma membrane) and diacylglycerol transferase enzyme (DGAT), as well as the inhibition of hormone-sensitive lipase-mediated lipolysis (Cianflone *et al.*, 2003). ASP also participates in the regulation of glucose homeostasis, since this hormone increases glucose-stimulated insulin secretion via a direct action on pancreatic β -cells (Ahren *et al.*, 2003). Elevated plasma ASP, C3 and adipsin concentrations have been found in obesity, type 1 and T2DM (Koistinen *et al.*, 2001; Cianflone *et al.*, 2003). Although plasma ASP concentrations are correlated inversely with insulin sensitivity, this association is lost in T2DM (Koistinen *et al.*, 2001). Taken together, ASP is associated with whole-body glucose and lipid metabolism in healthy individuals, whereas metabolic disturbances in obesity and T2DM may overcome the regulatory role of ASP in lipid and glucose homeostasis.

Only C3 and, to a lesser extent, ASP have been examined with respect to CAD and dyslipidaemia. On the one hand, increased C3 levels are associated with hypertension and T2DM (with an additive effect) and C3 has been shown to be a powerful predictor of myocardial infarction (Muscarì *et al.*, 1995). On the other hand, ASP is increased in subjects with CAD, especially in those with increased plasma TG and/or cholesterol, as characterized by increased plasma apolipoprotein B levels (Cianflone *et al.*, 1997). Growing evidence supports a role for ASP and C3 in adipose tissue function and maintenance of whole-body glucose homeostasis (Cianflone *et al.*, 2003). The aetiology of the links between ASP and C3 with T2DM and CAD and well-recognized risk factors such as insulin resistance and lipid profile has not been disentangled completely and future studies are required to unravel the exact role of these molecules in the ethiopathogenesis of CVD.

Concluding Remarks

Given the current prevalence of obesity and that this condition is a major modifiable contributor to CHD, a better understanding of the underlying mechanisms that relate fat mass to cardiovascular health is of paramount importance. Adipose tissue constitutes an important source of circulating mediators of inflammation that participate in the mechanism of cardiovascular injury and atherogenesis. Adipocytes and adipose tissue-embedded macrophages secrete proinflammatory cytokines (TNF- α , IL-6), acute-phase reactants (CRP, SAA), complement factors (adipsin and ASP), prothrombotic molecules (PAI-1, tissue factor), growth factors (cardiotrophin-1, EGF, FGF) and hormones implicated in the regulation of inflammation (leptin, resistin, osteopontin, adiponectin). In addition, increased adiposity is accompanied by a defective lipid partitioning that favours the development of CVD. Excessive fatty acid release in obesity leads to lipid deposition in muscle, liver, pancreas and heart. This ectopic lipid accumulation contributes to the development of insulin resistance, atherogenic dyslipidaemia and hyperinsulinaemia.

The exact participation of the complex network of bioactive mediators on vasoactivity and inflammation remains to be disentangled fully, in particular as

regards gaining more insight into the mechanisms involved in the activation and integration of the diverse signalling pathways. Major advances in unravelling the molecular events underlying inflammation and atherogenesis are to be expected by focusing on how the known vasoactive factors are related to the more recently identified hormones, adipokines, receptors, channels and peptides such as obestatin, adrenomedullin, hypoxia-sensitive molecules, aquaporins, caveolins and caspases. Undoubtedly, given the adipose tissue's versatile and ever-expanding list of activities, additional and unexpected vasoactive peptides are sure to emerge. The intense ongoing epidemiological, interventional and molecular research warrants the incorporation of relevant and novel information in many different frontiers of our current cardiovascular knowledge.

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