Cardiovascular effects of leptin

Gary Sweeney

Abstract | A wealth of investigations, ranging from clinical and animal model studies to *in vitro* analyses, have generated great interest in the cardiovascular effects of leptin. Accordingly, many studies have examined the contribution of leptin to cardiac remodeling in heart failure and whether the effects of leptin on metabolism, apoptosis, extracellular matrix remodeling, and hypertrophy could explain the so-called obesity paradox. Furthermore, obesity and hyperleptinemia have often been associated with hypertension, and regulation of sympathetic tone or direct effects of leptin on contributors such as atherosclerosis, endothelial dysfunction, and thrombosis have been documented. Unfortunately, translating basic research studies *in vitro,* or in animal models, to human physiology has proven difficult. The degree of leptin resistance in obesity is one intriguing issue that must be resolved. Furthermore, the importance of autocrine and paracrine effects of leptin derived from the heart and perivascular adipose tissue must be further studied. Carefully planned and executed research to conclusively establish distinct effects of leptin on the cardiovascular system in normal and diseased states will be essential to harness any therapeutic potential associated with leptin's effects.

Sweeney, G. *Nat. Rev. Cardiol*. **7**, 22–29 (2010); published online 1 December 2009; doi:10.1038/nrcardio.2009.224

Introduction

Much effort has been expended to establish associations between obesity and various aspects of cardiovascular disease, and to understand the underlying pathophysiological mechanisms. Such studies have highlighted the mechanistic complexity and temporal nature of cardiovascular disease, such that many apparently conflicting observations have been reported. For example, obese individuals are more likely to suffer myocardial infarction (MI), yet an obesity paradox exists since these patients often have improved post-MI event-free survival.[1] Whether leptin—the product of the obesity gene—exerts beneficial or detrimental effects on cardiovascular function has been extensively investigated and yielded many valuable, yet often paradoxical, observations.[1,2]

This Review will briefly describe the main effects of leptin on various aspects of cardiovascular function and discuss some of the proposed underlying mechanisms. Several novel and emerging concepts in this established area of research will also be discussed. Finally, steps required to harness the therapeutic potential of manipulating leptin-mediated cardiovascular effects will be highlighted. The goal of this Review is to update current knowledge pertaining to the cardiovascular effects of leptin, provide interpretation and perspective on their physiological and pathophysiological significance—especially in light of the many paradoxical observations in published literature—and to provoke discussion on the major outstanding questions.

Sources of leptin

On the basis of work on experimental rodent models, leptin was initially thought to be an antiobesity hormone, but the discovery of leptin resistance showed this belief to be too simplistic. In humans, plasma leptin levels typically correlate with fat mass and are altered by changes in energy balance. Indeed, leptin is traditionally viewed as a product of adipocytes that can exert endocrine effects. However, several peripheral tissues, including the heart, are now known to also produce leptin (Box 1), which might then mediate functional autocrine or paracrine effects.[3,4] Localized depots, such as epicardial or perivascular fat, may also make significant physiological and pathological contributions, as discussed below.

Epicardial adipose tissue from patients with coronary artery disease has higher leptin levels than that from individuals without coronary artery disease.[5] Furthermore, correlations have been found between myocardial function and the increased epicardial fat mass observed in obese individuals,[6–10] and decreases in epicardial fat mass can occur after weight loss, bariatric surgery, or exercise training.[11–13] From a research perspective, small animal models are not ideally suited for studying the role of epicardial fat, since virtually no epicardial fat is found in healthy mice and rats and epicardial fat that is present in obese rodents is localized around the pericardium, rather than being in direct contact with the heart muscle, as seen in humans.

Perivascular adipose tissue is likely to have a greatly underappreciated role in mediating vascular function.[14–16] In pathological states, this fat depot is thought to secrete a deleterious profile of adipokines, and leptin levels in perivascular fat have been hypothesized to increase.[14,16] Indeed, adipokine mixtures derived from perivascular adipose tissue from aged or obese models have been shown to stimulate proliferation of smooth muscle cells to a greater degree than mixtures from control animal tissue.[17] Importantly, however, the effect on proliferation

Institut Pasteur Korea, Sampyeong-dong 696, Bundang-gu, Gyeonggi-do, Korea.
Department of Biology, York University, 4700 Keele St, Toronto, ON M3J 1P3, Canada.
gsweeney@yorku.ca

Competing interests
The author declares no competing interests

of smooth muscle cells was not seen when applying mixtures taken from obese Zucker rats, which have a defective leptin receptor rather than abnormal leptin production, implicating a role for leptin signaling in this process.[17]

Leptin and cardiovascular disease

Leptin is known to have a role in regulating appetite and, therefore, weight gain by signaling the level of satiety to the brain.[18] In general, most obese individuals have elevated circulating levels of leptin and the prevailing hypothesis is that the elevated leptin levels correlate with leptin resistance in these individuals (Figure 1).[19,20] Many studies have shown correlations between circulating leptin levels and various cardiovascular outcomes.[21] In general, the elevated circulating levels of leptin found in most obese individuals correlate with unfavorable outcomes in end points such as hypertension, atherosclerosis, MI, stroke, inflammation, and angiogenesis. However, paradoxical observations also often exist for each of these cases.

Leptin-deficient *ob*/*ob* mice have been the most commonly studied animal model of obesity. In these mice, left ventricular (LV) function varies with age; LV contraction and relaxation (dP/dt) are high in young animals (4–5 weeks of age)—even in the presence of significant obesity—but in 10 to 11-week-old *ob*/*ob* mice, diastolic dysfunction occurs, as demonstrated by reduced E/A ratios.[22,23] Similar findings have been reported in *db*/*db* mice, which are deficient in leptin receptor function; systolic and diastolic dysfunction occur in 12-week-old mice but not in 6-week-old mice.[24] Cardiac dysfunction also occurs in adult obese Zucker rats, which have a leptin receptor defect.[25] Leptin was also shown to stimulate platelet aggregation, thus lower levels of thrombus formation are observed in *ob*/*ob* mice, which also tend to show some resistance to atherosclerosis.[26–28]

Although the above-mentioned animal models have been extensively used, caution must be applied when interpreting results, since leptin deficiency and leptin receptor mutations are extremely rare in cases of human obesity. Indeed, although supplementing leptin reversed the obese phenotype in ob/ob mice, leptin therapy has been largely ineffective in treating human obesity and associated complications, which are thought to mostly occur as a result of leptin resistance.[29]

As mentioned above, the majority of obese individuals are hyperleptinemic and the prevailing hypothesis is that leptin resistance results in defective hypothalamic regulation of food intake in obese humans.[19,20] However, observations that satiety and energy metabolism were resistant to leptin in obese individuals, but that leptin's sympathoexcitatory actions were maintained, have led some researchers to suggest that the leptin resistance might not be a ubiquitous phenomenon.[19,30] If this hypothesis is true, hyperleptinemia in obese individuals might result in enhanced leptin action in some tissues. Whether the heart becomes leptin resistant in pathogenic states is currently unclear. Nevertheless, one study has demonstrated that ventricular cardiomyocytes isolated from rats subjected to 10-week dietary sucrose feeding (to generate hyperleptinemia and insulin resistance) have impaired leptin signaling,[31] suggesting the development of cardiac leptin resistance. On the other hand, many of the cardiovascular effects of leptin are detrimental rather than cardioprotective (as discussed below), so it would seem logical that some of the cardiovascular pathology seen in obese individuals might result from the excess leptin rather than from cardiovascular leptin resistance. It could thus be postulated that specific leptin-mediated effects might become leptin resistant whilst others might remain leptin sensitive.

Leptin can impact upon cardiovascular function via direct effects on the heart (Figure 2) and vessels (Figure 3) or via secondary responses mediated by the central nervous system. Interestingly, too much and too little leptin signaling leads to adverse cardiovascular effects. To maintain a homeostatic environment, a feedback loop exists—which involves, for example, induction of SOCS-3 (suppressor of cytokine signaling 3) expression—to dampen any excessive leptin action. If this feedback system is not properly regulated, however, leptin resistance may occur.

Key points

- Leptin regulates various cardiovascular effects, yet many paradoxical observations have been reported and several controversies remain
- Reasons for these discrepancies may include the temporal nature of cardiovascular disease, actual leptin concentration examined, and the degree of crosstalk with other cardioregulatory factors
- Leptin resistance is thought to develop in obese individuals, yet may be selective to only a subset of the physiological effects of leptin
- Excess or inadequate leptin signaling are likely to result in unfavorable outcomes, and the maintenance of homeostatic leptin effects may be a beneficial treatment strategy
- The myocardium and perivascular adipose tissue are known sources of leptin, which might exert important autocrine and paracrine effects

Box 1 | Sources of leptin

- Cardiac tissue
- Epicardial fat
- Perivascular fat
- Subcutaneous fat
- Visceral fat
- Placenta
- Stomach

Direct effects of leptin on the heart

Metabolic effects

Reduced glucose oxidation rates and increased fatty acid oxidation rates are typically observed in hearts of obese individuals.[1,32] These alterations in cardiac metabolism are some of the first measurable abnormalities in failing hearts and probably critical in mediating subsequent contractile dysfunction.[22] Many studies have shown the potential for leptin to contribute to these changes.

In isolated working rat hearts, leptin has been shown to increase fatty acid oxidation rates, a response

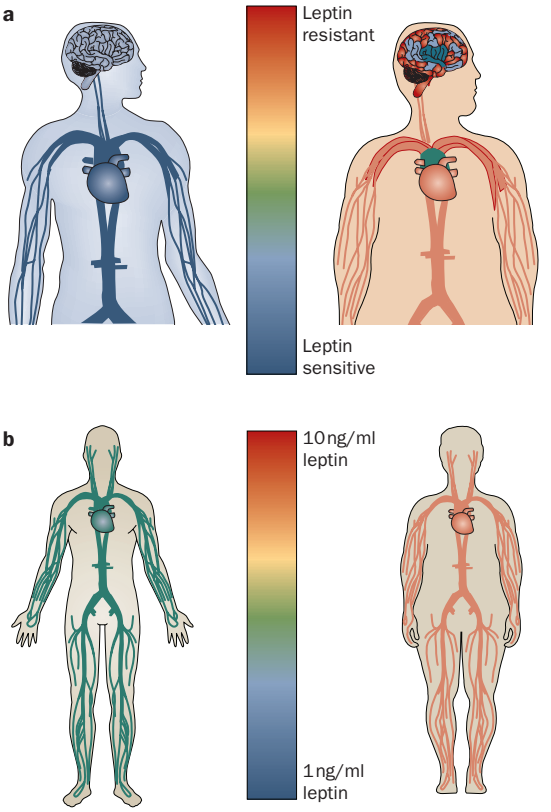

Figure 1 | Altered leptin sensitivity and circulating levels of leptin in obese individuals. **a** | The degree of leptin sensitivity in various regions of the body, as depicted by the color range indicated. Although the heart and peripheral tissue of an obese individual are thought to be leptin resistant in general, some areas may remain sensitive. **b** | Low to high circulating leptin levels (colored scale represents ~1 ng/ml to 10 ng/ml) in lean and obese individuals. Elevated leptin levels in obese individuals are thought to result from leptin resistance.

accompanied by an increase in myocardial oxygen consumption and, therefore, decreasing cardiac efficiency.[33] A detailed analysis of fatty acid oxidation has demonstrated that leptin acts to stimulate oxidation via a pathway involving signal transducer and activator of transcription 3, nitric oxide (NO), and p38 mitogen activated protein kinase (MAPK).[34] These effects of leptin could be viewed as unfavorable.

Notably, leptin treatment of murine cardiomyocytes has been shown to cause increases in fatty acid uptake as well as short-term increases in fatty acid oxidation, but the latter were followed by long-term decreases in oxidation, leading to intracellular lipid accumulation.[35] Zucker rat hearts also exhibit increased uptake of fatty acids, which was found to result from an increase in plasma membrane content of fatty acid transporters.[36,37] However, Zucker rats do not upregulate cardiac fatty acid oxidation in response to increasing delivery of fatty acids, which leads to accumulation of myocardial triglycerides and lipotoxicity.[25,38] Importantly, studies in human autopsy tissue have demonstrated the existence of lipid accumulation in human hearts, thus providing strong evidence for the pathophysiological significance of this phenomenon.[38–40] Hearts of *ob*/*ob* mice have an increased capacity to oxidize fatty acids in response to increasing delivery of fatty-acid substrates, which exceeds that of wildtype hearts.[41] This observation seems to be inconsistent with those in other models.

Leptin has been shown to have no effect on glucose uptake or metabolism in murine cardiomyocytes,[35] and to have no effect on glucose oxidation in isolated working rat hearts.[33] Similarly, intravenous or intracerebroventricular infusion of leptin in mice had no effect on cardiac glucose uptake.[42] In contrast to these findings, however, a study of Langendorff-perfused rat hearts showed that leptin stimulated glucose uptake,[43] and in Zucker rats, a reduction in glucose (and lactate) metabolism has been described even before the onset of hyperglycemia.[44,45]

Obviously, we do not yet fully understand the various metabolic effects of leptin, nor which of these effects mediate cardiovascular pathology. Given the importance of metabolic perturbations in cardiac dysfunction, further delineation of leptin's metabolic effects might provide potential new avenues of therapeutic development.

Apoptotic effects

Myocyte apoptosis plays an important role in the development of heart failure, particularly in the transition from compensatory remodeling to heart failure.[46] Evidence of apoptotic cardiomyocyte death was observed in endomyocardial biopsies from patients with dilated or ischemic cardiomyopathy and end-stage heart failure.[47,48] Additionally, cardiomyocytes isolated from failing human hearts showed increased susceptibility to hypoxia-induced apoptosis.[49] Various contractile proteins (α-actin, α-actinin, α/β-myosin heavy chain, tropomyosin, and troponins) can be cleaved by proteases in the apoptotic cascade, which has perhaps been underappreciated and could also contribute substantially to deterioration in contractile function.[50,51]

Leptin can protect cardiomyocytes from apoptosis induced by hypoxia-reoxygenation or H_2O_2.[52,53] Apoptosis induced by chronic ischemia *in vivo* can also be attenuated by leptin.[54] Although the issue remains somewhat contentious, a large body of evidence clearly identifies apoptosis as a potentially important contributor to myocardial dysfunction and early mortality in leptin-deficient and leptin-receptor-deficient animal models. For example, in several such models increased levels of apoptosis and DNA damage, and reduced DNA repair were observed and correlated with decreased survival.[55] Intact leptin signaling, notably phosphatidylinositol-3 kinase, was shown to be required to prevent age-associated increases in cardiomyocyte apoptosis in *ob*/*ob* and *db*/*db* mice.[56] Leptin administration has been shown to reduce the infarct area after ischemia–reperfusion injury *ex vivo*.[57] Studies in Zucker fatty rats have shown increased apoptosis that was associated with increased cardiomyocyte levels of ceramide and triglycerides.[58] Leptin, acting via Akt and extracellular regulated kinase 1/2, also lowered the infarct size in isolated control, but not *fa*/*fa* Zucker rat hearts subjected to

ischemia–reperfusion injury.[59] Thus, available data indicates that leptin confers cardioprotection via attenuating cardiomyocyte apoptosis.

Hypertrophic effects

The degree of heart failure, regardless of differing etiologies, is associated with a progressive enlargement of the left ventricle.[60,61] Although it represents an initially favorable adaptive mechanism, hypertrophy ultimately translates to a maladaptive process that contributes to acceleration of myocardial dysfunction.[62,63] Many researchers have consistently provided strong evidence that leptin directly induces hypertrophy in both human and rodent cardiomyocytes,[3,64–70] although one study failed to detect any leptin-induced change in LV mass.[71] Changes in hypertrophy were demonstrated to be of functional consequence in diet-induced obesity,[72] and a leptin-receptor-neutralizing antibody improved cardiac function in rats subjected to coronary artery ligation.[73] Leptin mediates hypertrophy at least in part through a p38 MAPK-dependent signaling pathway,[65,68,69,74] which is indeed characteristic of pathological evidence in hypertrophied hearts.[75,76]

A somewhat contradictory exaggerated hypertrophic response to coronary artery ligation was observed in *ob*/*ob* compared to control mice,[77] and infusion of leptin to *ob*/*ob* mice decreased the exaggerated left ventricular wall thickness.[78] The data described here raise the interesting possibility that too much or too little leptin contributes to pathophysiological hypertrophy in some cases of obesity.

Effects on the extracellular matrix

The main components of the cardiac extracellular matrix (ECM) are often described as structural (for example, collagen and elastic fibers) and adhesive (for example, fibronectin and laminin) and turnover of collagen is regulated by the family of matrix metalloproteinases (MMPs).[79–81] Alterations in the composition and structure of the ECM make an important contribution to changes in cardiac size, structure and function in heart failure.[82] The effects of leptin on ECM components in the cardiovascular system are relatively underexplored and may prove fruitful in establishing viable targets to manipulate therapeutically.

To date, only a few studies have shown that leptin can influence cardiac ECM remodeling and more work is definitely required, particularly on the temporal nature of leptin's effects, which may be of great importance.[82] Both cardiac fibroblasts and cardiomyocytes make substantial, but distinct, contributions to ECM synthesis and turnover. In primary human pediatric ventricular myocytes, leptin increases procollagen type-III and type-IV mRNA and decreases procollagen type-I levels, but does not change total collagen synthesis.[64] In neonatal rat fibroblasts, intracellular and secreted procollagen type-I levels are increased and procollagen type-III levels are decreased in response to leptin.[83] Increased fibrosis has been described in the hearts of *ob*/*ob* mice and in Zucker (*fa*/*fa*) rats.[58,84–86] Coronary artery ligation caused an elevation in procollagen type-I and procollagen type-III mRNA expression at 7 days postinfarction and the contribution of leptin-mediated effects was demonstrated by the observation that enhanced collagen was attenuated following infusion with a neutralizing leptin receptor antibody.[73]

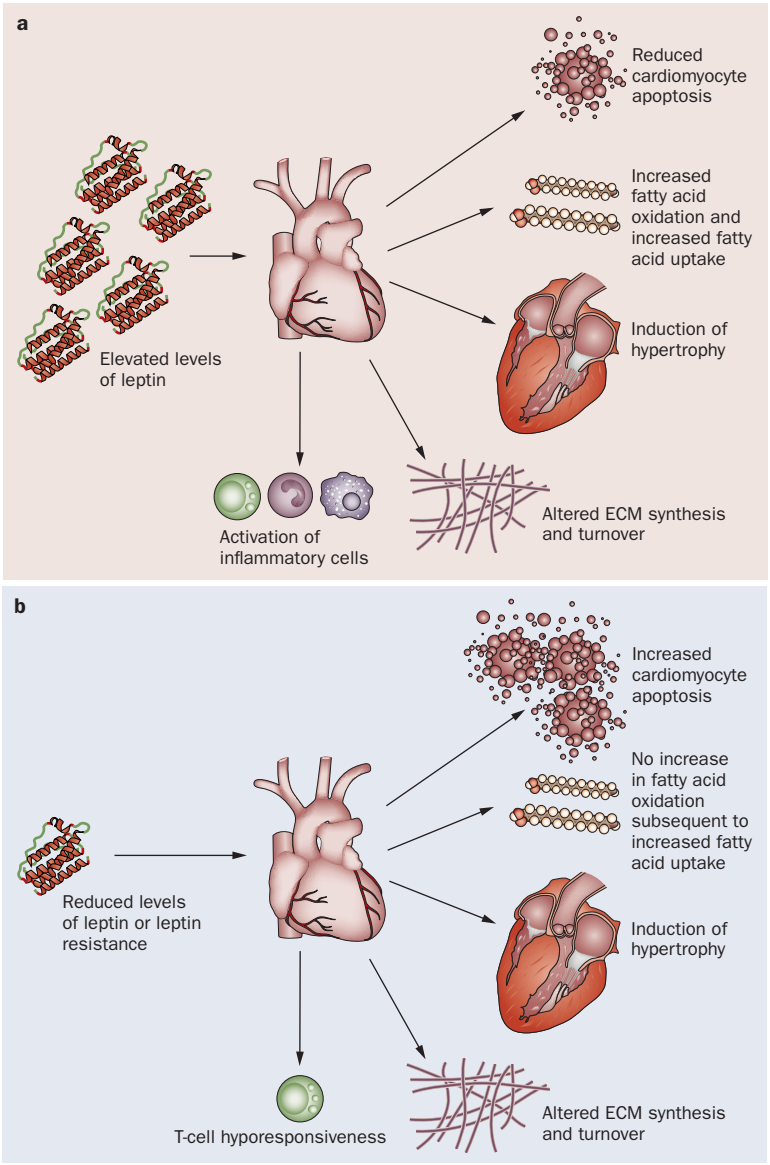

Figure 2 | Direct effects of leptin on the heart. **a** | Effects of elevated levels of leptin. **b** | Effects of reduced levels of leptin or leptin resistance.

Leptin directly stimulated MMP-2 expression and activity in neonatal rat cardiac myofibroblasts,[83] and in pediatric ventricular cardiomyocytes,[64] again, at least in part, via p38 MAPK. Serum and myocardial leptin levels and leptin receptor (ObR) mRNA expression were elevated upon coronary artery ligation, and this correlated with upregulated MMP-2 and MMP-9 mRNA and decreased tissue inhibitor of MMP (TIMP)-1 and TIMP-2 mRNA expression.[87]

Inflammatory effects

The cardiovascular consequences of inflammation are well established and many studies have correlated increased levels of proinflammatory cytokines with

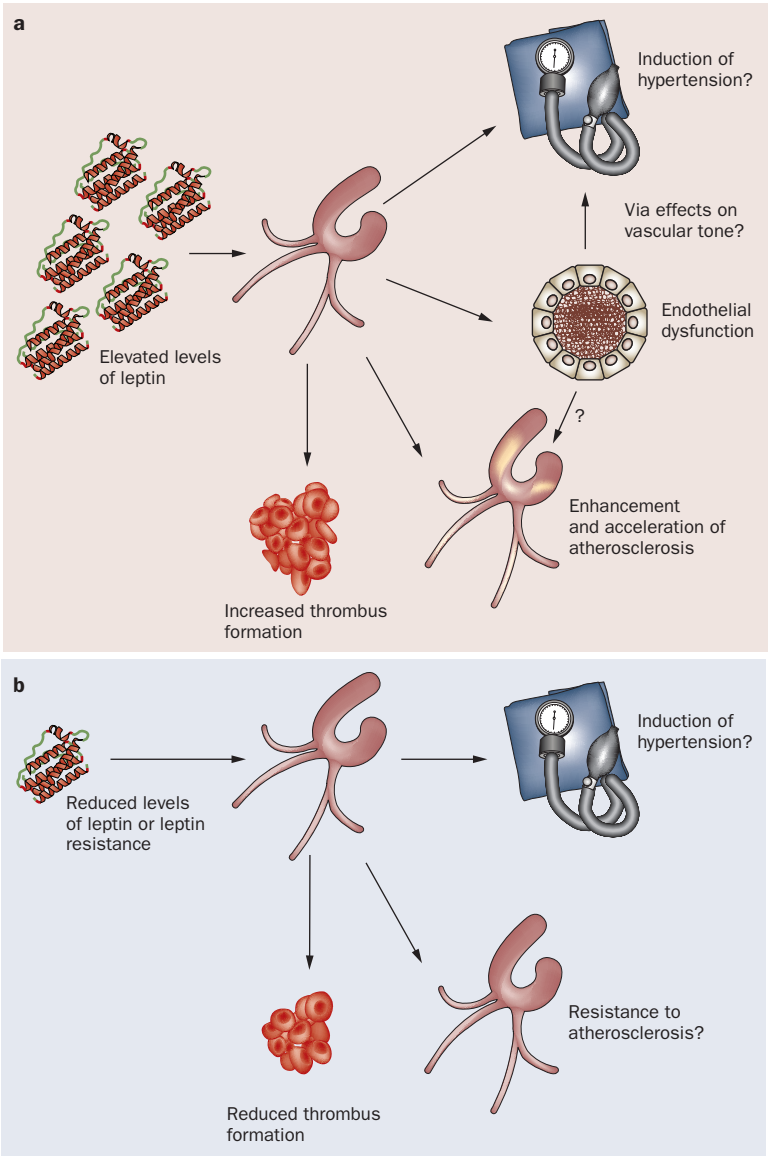

Figure 3 | Direct effects of leptin on the vasculature. **a** | Effects of elevated levels of leptin. **b** | Effects of reduced levels of leptin or leptin resistance.

adverse outcomes. In particular, inflammatory factors produced by cells of the myocardium (cardiomyocytes, endothelial cells, fibroblasts, and smooth muscle cells) and by infiltrating leukocytes, platelets, and macrophages can impact on the structure and function of the myocardium, and systemic inflammation also impacts on vascular function.[88–90]

Leptin may be one of the important pathophysiological mediators of inflammation and was even proposed to physically interact with C-reactive protein, although substantiating this phenomenon has proven to be rather controversial. Great interest currently surrounds the connection between innate immunity and inflammation in heart failure, and toll-like receptors are likely to have a central role.[91,92] Notably, leptin is a potent regulator of toll-like receptor expression.[93] Leptin, itself, seems to be induced as a consequence of innate immune system activation, and leptin receptor signaling activates T-lymphocytes, macrophages, and monocytes.[19] Furthermore, leptin deficiency in humans or animal models is associated with T-cell hyporesponsiveness. Clearly, regulation of inflammatory mediators in the heart and vasculature by leptin can have a substantial influence on overall cardiovascular function.

Inflammatory components have been targeted in attempts to treat animals and humans with cardiovascular disease, but studies to date have employed anti-TNF therapeutic approaches and have thus far proven largely ineffective. Targeting inflammation is likely to be more successful once we understand more about hormones such as leptin and the specific cardiovascular consequences of their inflammatory effects.[94]

Direct vascular effects of leptin

Hypertensive effects

Obesity is typically associated with greater risk of hypertension and strong correlations exist between blood pressure and circulating leptin levels over a wide range of blood pressures.[95] One potential reason for these observations is that leptin resistance in obesity is selective to hypothalamic regulation of food intake and does not apply to the ability of leptin to stimulate central sympathetic activation. Subsequent peripheral outcomes would include an enhanced systemic pressor effect and a decreased kidney natriuresis, both contributing to hypertension.[96] This theory was reinforced by a study in which hypertension was induced by central overexpression of leptin and reversed by a leptin antagonist. However, leptin antagonism did not alter hypertension associated with high-fat feeding, which brings the pathophysiological significance of these findings into question.[97] Notably, the positive association between leptin and hypertension is by no means consistently reported and factors such as age, sex, and race may be contributing factors. Furthermore, leptin administration in healthy individuals does not exert a significant acute effect on blood pressure. Few studies have focused on hypertension in animal models but both obese *db*/*db* mice and Zucker rats show a propensity to develop hypertension.[98,99]

Atherosclerotic effects

Leptin enhances and accelerates atherosclerosis via various mechanisms, including stimulating intimal monocyte recruitment, macrophage-to-foam cell transformation, proliferation of vascular smooth muscle cells, and further secretion of proatherogenic cytokines.[28] Various *ob*/*ob*-based mouse models show resistance to atherosclerosis.[28] Furthermore, leptin directly increased atherosclerosis in apolipoprotein $E^{-/-}$ mice. Enhanced obR content has been detected in atherosclerotic lesions. An interesting study demonstrated that the proatherogenic effects of leptin on human monocytes occurred via phosphoinositide 3-kinase and conventional protein kinase C signaling and involved the actin cytoskeleton, Na^+/H^+ exchanger-1 and NADPH oxidase.[100]

As with many of the cardiovascular effects of leptin, data suggest that leptin can also protect against atherosclerosis. For example, LDL-$receptor^{-/-}$ *ob*/*ob* mice exhibit

a higher degree of atherosclerosis than LDL-receptor$^{-/-}$ mice. However, as discussed above, leptin deficiency is rarely seen in obese humans.

Mediation of endothelial dysfunction

Endothelial dysfunction is often viewed as a precursor to atherosclerotic disease. Although the literature contains several indications that leptin mediates this process, it should be stressed that endothelial dysfunction is typically observed at supraphysiological concentrations. Nevertheless, leptin caused an endothelial NO/ONOO$^-$ imbalance characteristic of dysfunctional endothelium.[101] Leptin may also mediate direct effects on vascular tone, for example high leptin concentrations can cause endothelium-dependent NO-mediated relaxation in rat vessels from control, but not obese, Zucker rats.[102] Furthermore, an interactive link with the inflammatory state is indicated by the observation that leptin acting via 5'-AMP-activated protein kinase and Akt signaling to induce endothelial NO synthase was attenuated by C-reactive protein.[103] Interestingly, decreases in endothelial-dependent coronary artery dilation in response to acetylcholine, normally mediated by leptin, were not observed in leptin-resistant dogs fed a high-fat diet.[104]

Thrombosis induction

Thrombus formation is a principal cause of acute coronary events, particularly in obese individuals.[105] Many studies have shown that leptin increases platelet aggregation, with one interesting suggestion being that this observation may be concentration dependent, with only high leptin levels being prothrombotic.[106] Indeed, platelets from obese patients are leptin sensitive and have enhanced ADP-induced aggregation, compared with platelets from lean patients.[107] Animal model studies also provide evidence for a prothrombotic effect of leptin; for example, lower levels of thrombus formation are observed in *ob*/*ob* mice, but this observation is reversed by leptin supplementation.[26,27] The mechanism of leptin-induced platelet aggregation at least partly involves cGMP-inhibited 3',5'-cyclic phosphodiesterase 3A, which suggests there is potential for pharmacological intervention.[108]

Conclusions

Although many attractive theories on the effect of excess leptin action or leptin deficiency on the cardiovascular system have been proposed, numerous key questions remain to be answered. For example, in obesity, do the metabolic effects of leptin—which may generally be regarded as unfavorable—become elevated as a result of hyperleptinemia and explain the correlations between circulating leptin and risk of myocardial infarction? Do the antiapoptotic effects of leptin—which can be regarded as cardioprotective—become leptin resistant and also contribute to risk of infarction, or do these effects also become elevated in obese individuals? The latter option would explain the apparently protective effects conferred by obesity after myocardial infarction. Additionally, does leptin mediate distinct effects on ECM protein production and related degradative enzymes (from both fibroblasts and cardiomyocytes) at different stages in the progression of heart failure, perhaps depending on coexistence of hyperglycemia, hyperinsulinemia, or an inflammatory background? Does chronic hyperleptinemia cause hypertension, and if so, is this due to increased sympathetic tone, direct peripheral effects, or both? Do some of the direct effects of leptin on the cardiovascular system show different leptin sensitivity and only manifest in cases of hyperleptinemia? Is the significance of the interaction between leptin and innate immunity currently somewhat underestimated? These are just some of the intriguing questions that could be answered by appropriate future research in this area.

Studies that clearly establish the direct effects of leptin on the cardiovascular system and the mechanisms employed to mediate these effects may allow therapeutic exploitation of the cardioprotective effects of leptin while avoiding injurious outcomes. This knowledge could be applicable in cases of obesity, hyperleptinemia, and leptin resistance or lipodystrophic states where leptin is lacking.

Review criteria

A comprehensive search for full-text English language articles on the PubMed database was performed to find articles published to August 2009. Keywords included "leptin", "cardiovascular", and "heart". The cited papers were selected on the basis of their relevance and fit with the topic of this Review. Cited references were also used as a source for additional relevant publications. Regrettably, many relevant papers in the field were not quoted owing to space limitation.

1. Abel, E. D., Litwin, S. E. & Sweeney, G. Cardiac remodeling in obesity. *Physiol. Rev.* **88**, 389–419 (2008).
2. Sweeney, G. Unraveling the mechanisms linking obesity and heart failure: the role of adipokines. *Expert Rev. Endocrinol. Metab.* **4**, 95–97 (2009).
3. Rajapurohitam, V., Javadov, S., Purdham, D. M., Kirshenbaum, L. A. & Karmazyn, M. An autocrine role for leptin in mediating the cardiomyocyte hypertrophic effects of angiotensin II and endothelin-1. *J. Mol. Cell. Cardiol.* **41**, 265–274 (2006).
4. Purdham, D. M., Zou, M. X., Rajapurohitam, V. & Karmazyn, M. Rat heart is a site of leptin production and action. *Am. J. Physiol. Heart Circ. Physiol.* **287**, H2877–H2884 (2004).
5. Cheng, K. H. *et al.* Adipocytokines and proinflammatory mediators from abdominal and epicardial adipose tissue in patients with coronary artery disease. *Int. J. Obes. (Lond.)* **32**, 268–274 (2008).
6. Rabkin, S. W. Epicardial fat: properties, function and relationship to obesity. *Obes. Rev.* **8**, 253–261 (2007).
7. Silaghi, A. *et al.* Epicardial adipose tissue extent: relationship with age, body fat distribution, and coronaropathy. *Obesity (Silver Spring)* **16**, 2424–2430 (2008).
8. Sarin, S. *et al.* Clinical significance of epicardial fat measured using cardiac multislice computed tomography. *Am. J. Cardiol.* **102**, 767–771 (2008).
9. Iacobellis, G. *et al.* Influence of excess fat on cardiac morphology and function: study in uncomplicated obesity. *Obes. Res.* **10**, 767–773 (2002).
10. Iacobellis, G. & Leonetti, F. Epicardial adipose tissue and insulin resistance in obese subjects. *J. Clin. Endocrinol. Metab.* **90**, 6300–6302 (2005).
11. Kim, M. K. *et al.* Aerobic exercise training reduces epicardial fat in obese men. *J. Appl. Physiol.* **106**, 5–11 (2009).
12. Willens, H. J. *et al.* Effects of weight loss after bariatric surgery on epicardial fat measured using echocardiography. *Am. J. Cardiol.* **99**, 1242–1245 (2007).
13. Iacobellis, G., Singh, N., Wharton, S. & Sharma, A. M. Substantial changes in epicardial fat thickness after weight loss in severely obese subjects. *Obesity (Silver Spring)* **16**, 1693–1697 (2008).

14. Iacobellis, G., Gao, Y. J. & Sharma, A. M. Do cardiac and perivascular adipose tissue play a role in atherosclerosis? *Curr. Diab. Rep.* **8**, 20–24 (2008).
15. Stern, N. & Marcus, Y. Perivascular fat: innocent bystander or active player in vascular disease? *J. Cardiometab. Syndr.* **1**, 115–120 (2006).
16. Knudson, J. D., Payne, G. A., Borbouse, L. & Tune, J. D. Leptin and mechanisms of endothelial dysfunction and cardiovascular disease. *Curr. Hypertens. Rep.* **10**, 434–439 (2008).
17. Barandier, C., Montani, J. P. & Yang, Z. Mature adipocytes and perivascular adipose tissue stimulate vascular smooth muscle cell proliferation: effects of aging and obesity. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H1807–H1813 (2005).
18. Ahima, R. S. & Flier, J. S. Leptin. *Annu. Rev. Physiol.* **62**, 413–437 (2000).
19. Martin, S. S., Qasim, A. & Reilly, M. P. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. *J. Am. Coll. Cardiol.* **52**, 1201–1210 (2008).
20. Enriori, P., Evans, A. E., Sinnayah, P. & Cowley, M. A. Leptin resistance and obesity. *Obesity (Silver Spring)* **14**, 254S–258S (2006).
21. Koh, K. K., Park, S. M. & Quon, M. J. Leptin and cardiovascular disease: response to therapeutic interventions. *Circulation* **117**, 3238–3249 (2008).
22. Buchanan, J. *et al.* Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology* **146**, 5341–5349 (2005).
23. Christoffersen, C. *et al.* Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. *Endocrinology* **144**, 3483–3490 (2003).
24. Semeniuk, L. M., Kryski, A. J. & Severson, D. L. Echocardiographic assessment of cardiac function in diabetic db/db and transgenic db/db-hGLUT4 mice. *Am. J. Physiol. Heart Circ. Physiol.* **283**, H976–H982 (2002).
25. Young, M. E. *et al.* Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. *Diabetes* **51**, 2587–2595 (2002).
26. Konstantinides, S., Schafer, K., Koschnick, S. & Loskutoff, D. J. Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. *J. Clin. Invest.* **108**, 1533–1540 (2001).
27. Bodary, P. F., Westrick, R. J., Wickenheiser, K. J., Shen, Y. & Eitzman, D. T. Effect of leptin on arterial thrombosis following vascular injury in mice. *JAMA* **287**, 1706–1709 (2002).
28. Beltowski, J. Leptin and atherosclerosis. *Atherosclerosis* **189**, 47–60 (2006).
29. Bell-Anderson, K. S. & Bryson, J. M. Leptin as a potential treatment for obesity: progress to date. *Treat. Endocrinol.* **3**, 11–18 (2004).
30. Correia, M. L. & Rahmouni, K. Role of leptin in the cardiovascular and endocrine complications of metabolic syndrome. *Diabetes Obes. Metab.* **8**, 603–610 (2006).
31. Hintz, K. K., Aberle, N. S. & Ren, J. Insulin resistance induces hyperleptinemia, cardiac contractile dysfunction but not cardiac leptin resistance in ventricular myocytes. *Int. J. Obes. Relat. Metab. Disord.* **27**, 1196–1203 (2003).
32. Lopaschuk, G. D., Folmes, C. D. & Stanley, W. C. Cardiac energy metabolism in obesity. *Circ. Res.* **101**, 335–347 (2007).
33. Atkinson, L. L., Fischer, M. A. & Lopaschuk, G. D. Leptin activates cardiac fatty acid oxidation independent of changes in the AMP-activated protein kinase-acetyl-CoA carboxylase-malonyl-CoA axis. *J. Biol. Chem.* **277**, 29424–29430 (2002).
34. Sharma, V. *et al.* Stimulation of cardiac fatty acid oxidation by leptin is mediated by a nitric oxide-p38 MAPK-dependent mechanism. *Eur. J. Pharmacol.* **617**, 113–117 (2009).
35. Palanivel, R., Eguchi, M., Shuralyova, I., Coe, I. & Sweeney, G. Distinct effects of short- and long-term leptin treatment on glucose and fatty acid uptake and metabolism in HL-1 cardiomyocytes. *Metabolism* **55**, 1067–1075 (2006).
36. Berk, P. D. *et al.* Uptake of long chain free fatty acids is selectively up-regulated in adipocytes of Zucker rats with genetic obesity and non-insulin-dependent diabetes mellitus. *J. Biol. Chem.* **272**, 8830–8835 (1997).
37. Luiken, J. J. *et al.* Increased rates of fatty acid uptake and plasmalemmal fatty acid transporters in obese Zucker rats. *J. Biol. Chem.* **276**, 40567–40573 (2001).
38. Sharma, S. *et al.* Intramyocardial lipid accumulation in the failing human heart resembles the lipotoxic rat heart. *FASEB J.* **18**, 1692–1700 (2004).
39. McGavock, J. M., Victor, R. G., Unger, R. H. & Szczepaniak, L. S. Adiposity of the heart, revisited. *Ann. Intern. Med.* **144**, 517–524 (2006).
40. Szczepaniak, L. S. *et al.* Myocardial triglycerides and systolic function in humans: *in vivo* evaluation by localized proton spectroscopy and cardiac imaging. *Magn. Reson. Med.* **49**, 417–423 (2003).
41. Mazumder, P. K. *et al.* Impaired cardiac efficiency and increased fatty acid oxidation in insulin-resistant ob/ob mouse hearts. *Diabetes* **53**, 2366–2374 (2004).
42. Kamohara, S., Burcelin, R., Halaas, J. L., Friedman, J. M. & Charron, M. J. Acute stimulation of glucose metabolism in mice by leptin treatment. *Nature* **389**, 374–377 (1997).
43. Haap, M. *et al.* Insulin-like effect of low-dose leptin on glucose transport in Langendorff rat hearts. *Exp. Clin. Endocrinol. Diabetes* **111**, 139–145 (2003).
44. Wang, P., Lloyd, S. G., Zeng, H., Bonen, A. & Chatham, J. C. Impact of altered substrate utilization on cardiac function in isolated hearts from Zucker diabetic fatty rats. *Am. J. Physiol. Heart Circ. Physiol.* **288**, H2102–H2110 (2005).
45. Golfman, L. S. *et al.* Activation of PPARgamma enhances myocardial glucose oxidation and improves contractile function in isolated working hearts of ZDF rats. *Am. J. Physiol. Endocrinol. Metab.* **289**, E328–E336 (2005).
46. Lee, Y. & Gustafsson, A. B. Role of apoptosis in cardiovascular disease. *Apoptosis* **14**, 536–548 (2009).
47. Narula, J. *et al.* Apoptosis in myocytes in end-stage heart failure. *N. Engl. J. Med.* **335**, 1182–1189 (1996).
48. Olivetti, G. *et al.* Apoptosis in the failing human heart. *N. Engl. J. Med.* **336**, 1131–1141 (1997).
49. Todor, A. *et al.* Hypoxia-induced cleavage of caspase-3 and DFF45/ICAD in human failed cardiomyocytes. *Am. J. Physiol. Heart Circ. Physiol.* **283**, H990–H995 (2002).
50. Sung, M. M. *et al.* Matrix metalloproteinase-2 degrades the cytoskeletal protein alpha-actinin in peroxynitrite mediated myocardial injury. *J. Mol. Cell. Cardiol.* **43**, 429–436 (2007).
51. Communal, C. *et al.* Functional consequences of caspase activation in cardiac myocytes. *Proc. Natl Acad. Sci. USA* **99**, 6252–6256 (2002).
52. Shin, E. J., Schram, K., Zheng, X. L. & Sweeney, G. Leptin attenuates hypoxia/reoxygenation-induced apoptosis in rat H9c2 cardiomyocytes. *J. Cell. Physiol.* (in press).
53. Eguchi, M., Liu, Y., Shin, E. J. & Sweeney, G. Leptin protects H9c2 rat cardiomyocytes from H2O2-induced apoptosis. *FEBS J.* **275**, 3136–3144 (2008).
54. McGaffin, K. R., Zou, B., McTiernan, C. F. & O'Donnell, C. P. Leptin attenuates cardiac apoptosis after chronic ischaemic injury. *Cardiovasc. Res.* **83**, 313–324 (2009).
55. Barouch, L. *et al.* Cardiac myocytes apopotosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ. Res.* **98**, 119–124 (2006).
56. Trivedi, P., Yang, R. & Barouch, L. A. Decreased p110alpha catalytic activity accompanies increased myocyte apoptosis and cardiac hypertrophy in leptin deficient ob/ob mice. *Cell Cycle* **7**, 560–565 (2008).
57. Smith, C. C. *et al.* Leptin, the obesity-associated hormone, exhibits direct cardioprotective effects. *Br. J. Pharmacol.* **149**, 5–13 (2006).
58. Zhou, Y. T. *et al.* Lipotoxic heart disease in obese rats: implications for human obesity. *Proc. Natl Acad. Sci. USA* **97**, 1784–1789 (2000).
59. Dixon, R. A., Davidson, S. M., Wynne, A. M., Yellon, D. M. & Smith, C. C. The cardioprotective actions of leptin are lost in the Zucker obese (fa/fa) rat. *J. Cardiovasc. Pharmacol.* **53**, 311–317 (2009).
60. Florea, V. G. *et al.* Left ventricular remodelling: common process in patients with different primary myocardial disorders. *Int. J. Cardiol.* **68**, 281–287 (1999).
61. Cohn, J. N. Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition. *Circulation* **91**, 2504–2507 (1995).
62. Frey, N. & Olson, E. N. Cardiac hypertrophy: the good, the bad, and the ugly. *Annu. Rev. Physiol.* **65**, 45–79 (2003).
63. Frey, N., Katus, H. A., Olson, E. N. & Hill, J. A. Hypertrophy of the heart: a new therapeutic target? *Circulation* **109**, 1580–1589 (2004).
64. Madani, S., De Girolamo, S., Munoz, D. M., Li, R. K. & Sweeney, G. Direct effects of leptin on size and extracellular matrix components of human pediatric ventricular myocytes. *Cardiovasc. Res.* **69**, 716–725 (2006).
65. Rajapurohitam, V., Gan, X. T., Kirshenbaum, L. A. & Karmazyn, M. The obesity-associated peptide leptin induces hypertrophy in neonatal rat ventricular myocytes. *Circ. Res.* **93**, 277–279 (2003).
66. Xu, F. P. *et al.* Leptin induces hypertrophy via endothelin-1-reactive oxygen species pathway in cultured neonatal rat cardiomyocytes. *Circulation* **110**, 1269–1275 (2004).
67. Majumdar, P. *et al.* Leptin and endothelin-1 mediated increased extracellular matrix protein production and cardiomyocyte hypertrophy in diabetic heart disease. *Diabetes Metab. Res. Rev.* **25**, 452–463 (2009).
68. Zeidan, A., Javadov, S. & Karmazyn, M. Essential role of Rho/ROCK-dependent processes and actin dynamics in mediating leptin-induced hypertrophy in rat neonatal ventricular myocytes. *Cardiovasc. Res.* **72**, 101–111 (2006).
69. Zeidan, A., Javadov, S., Chakrabarti, S. & Karmazyn, M. Leptin-induced cardiomyocyte hypertrophy involves selective caveolae and RhoA/ROCK-dependent p38 MAPK translocation to nuclei. *Cardiovasc. Res.* **77**, 64–72 (2008).
70. Abe, Y. *et al.* Leptin induces elongation of cardiac myocytes and causes eccentric left ventricular dilatation with compensation. *Am. J. Physiol. Heart Circ. Physiol.* **292**, H2387–H2396 (2007).
71. Pinieiro, R. *et al.* Leptin does not induce hypertrophy, cell cycle alterations, or production of MCP-1 in cultured rat and mouse cardiomyocytes. *Endocr. Res.* **31**, 375–386 (2005).

72. Park, S. Y. *et al.* Unraveling the temporal pattern of diet-induced insulin resistance in individual organs and cardiac dysfunction in C57BL/6 mice. *Diabetes* **54**, 3530–3540 (2005).
73. Purdham, D. M. *et al.* A neutralizing leptin receptor antibody mitigates hypertrophy and hemodynamic dysfunction in the postinfarcted rat heart. *Am. J. Physiol. Heart Circ. Physiol.* **295**, H441–H446 (2008).
74. Madani, S., De Girolamo, S., Muñoz, D. M., Li, R. K. & Sweeney, G. Direct effects of leptin on size and extracellular matrix components of human pediatric ventricular myocytes. *Cardiovasc. Res.* **69**, 716–725 (2005).
75. Wakatsuki, T., Schlessinger, J. & Elson, E. L. The biochemical response of the heart to hypertension and exercise. *Trends Biochem. Sci.* **29**, 609–617 (2004).
76. Dorn, G. W. 2nd & Force, T. Protein kinase cascades in the regulation of cardiac hypertrophy. *J. Clin. Invest.* **115**, 527–537 (2005).
77. McGaffin, K. R. *et al.* Leptin signalling reduces the severity of cardiac dysfunction and remodelling after chronic ischaemic injury. *Cardiovasc. Res.* **77**, 54–63 (2008).
78. Barouch, L. A., Berkowitz, D. E., Harrison, R. W., O'Donnell, C. P. & Hare, J. M. Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. *Circulation* **108**, 754–759 (2003).
79. Fedak, P., Verma, S., Weisel, R. D. & Li, R. K. Cardiac remodeling and failure: From molecules to man (Part II). *Cardiovasc. Pathol.* **14**, 49–60 (2005).
80. Fedak, P., Verma, S., Weisel, R. D. & Li, R. K. Cardiac remodeling and failure: from molecules to man (Part I). *Cardiovasc. Pathol.* **14**, 1–11 (2005).
81. Graham, H. K., Horn, M. & Trafford, A. W. Extracellular matrix profiles in the progression to heart failure. European Young Physiologists Symposium Keynote Lecture-Bratislava 2007. *Acta Physiol. (Oxf.)* **194**, 3–21 (2008).
82. Schram, K. & Sweeney, G. Implications of myocardial matrix remodeling by adipokines in obesity-related heart failure. *Trends Cardiovasc. Med.* **18**, 199–205 (2008).
83. Schram, K. *et al.* Increased expression and cell surface localization of MT1-MMP plays a role in stimulation of MMP-2 activity by leptin in neonatal rat cardiac myofibroblasts. *J. Mol. Cell. Cardiol.* **44**, 874–881 (2008).
84. Zaman, A. K. *et al.* Angiotensin-converting enzyme inhibition attenuates hypofibrinolysis and reduces cardiac perivascular fibrosis in genetically obese diabetic mice. *Circulation* **103**, 3123–3128 (2001).
85. Zaman, A. K. *et al.* Salutary effects of attenuation of angiotensin II on coronary perivascular fibrosis associated with insulin resistance and obesity. *J. Mol. Cell. Cardiol.* **37**, 525–535 (2004).
86. Toblli, J. E., Cao, G., DeRosa, G. & Forcada, P. Reduced cardiac expression of plasminogen activator inhibitor 1 and transforming growth factor beta1 in obese Zucker rats by perindopril. *Heart* **91**, 80–86 (2005).
87. Xia, Q. *et al.* Improvement of chronic heart failure by dexamehtason is not associated with downregulation of leptin in rats. *Acta Pharmacologica Sinica* **28**, 202–210 (2007).
88. Parish, R. C. & Evans, J. D. Inflammation in chronic heart failure. *Ann. Pharmacother.* **42**, 1002–1016 (2008).
89. Yndestad, A. *et al.* Role of inflammation in the progression of heart failure. *Curr. Cardiol. Rep.* **9**, 236–241 (2007).
90. Yndestad, A. *et al.* Systemic inflammation in heart failure–the whys and wherefores. *Heart Fail. Rev.* **11**, 83–92 (2006).
91. Chao, W. Toll-like receptor signaling: a critical modulator of cell survival and ischemic injury in the heart. *Am. J. Physiol. Heart Circ. Physiol.* **296**, H1–H12 (2009).
92. Satoh, M., Ishikawa, Y., Minami, Y., Takahashi, Y. & Nakamura, M. Role of Toll like receptor signaling pathway in ischemic coronary artery disease. *Front. Biosci.* **13**, 6708–6715 (2008).
93. Batra, A. *et al.* Leptin-dependent toll-like receptor expression and responsiveness in preadipocytes and adipocytes. *Am. J. Pathol.* **170**, 1931–1941 (2007).
94. Heymans, S. *et al.* Inflammation as a therapeutic target in heart failure? A scientific statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **11**, 119–129 (2009).
95. Haynes, W. G. Role of leptin in obesity-related hypertension. *Exp. Physiol.* **90**, 683–688 (2005).
96. Rahmouni, K., Morgan, D. A., Morgan, G. M., Mark, A. L. & Haynes, W. G. Role of selective leptin resistance in diet-induced obesity hypertension. *Diabetes* **54**, 2012–2018 (2005).
97. Tumer, N., Erdos, B., Matheny, M., Cudykier, I. & Scarpace, P. J. Leptin antagonist reverses hypertension caused by leptin overexpression, but fails to normalize obesity-related hypertension. *J. Hypertens.* **25**, 2471–2478 (2007).
98. Su, W. *et al.* Hypertension and disrupted blood pressure circadian rhythm in type 2 diabetic db/db mice. *Am. J. Physiol. Heart Circ. Physiol.* **295**, H1634–H1641 (2008).
99. Osmond, J. M., Mintz, J. D., Dalton, B. & Stepp, D. W. Obesity increases blood pressure, cerebral vascular remodeling, and severity of stroke in the Zucker rat. *Hypertension* **53**, 381–386 (2009).
100. Konstantinidis, D., Paletas, K., Koliakos, G. & Kaloyianni, M. Signaling components involved in leptin-induced amplification of the atherosclerosis-related properties of human monocytes. *J. Vasc. Res.* **46**, 199–208 (2009).
101. Korda, M., Kubant, R., Patton, S. & Malinski, T. Leptin-induced endothelial dysfunction in obesity. *Am. J. Physiol. Heart Circ. Physiol.* **295**, H1514–H1521 (2008).
102. Knudson, J. D. *et al.* Leptin receptors are expressed in coronary arteries, and hyperleptinemia causes significant coronary endothelial dysfunction. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H48–H56 (2005).
103. Procopio, C. *et al.* Leptin-stimulated endothelial nitric-oxide synthase via an adenosine 5'-monophosphate-activated protein kinase/Akt signaling pathway is attenuated by interaction with C-reactive protein. *Endocrinology* **150**, 3584–3593 (2009).
104. Knudson, J. D. *et al.* Leptin resistance extends to the coronary vasculature in prediabetic dogs and provides a protective adaptation against endothelial dysfunction. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H1038–H1046 (2005).
105. Bodary, P. F. Links between adipose tissue and thrombosis in the mouse. *Arterioscler. Thromb. Vasc. Biol.* **27**, 2284–2291 (2007).
106. Nakata, M., Yada, T., Soejima, N. & Maruyama, I. Leptin promotes aggregation of human platelets via the long form of its receptor. *Diabetes* **48**, 426–429 (1999).
107. Dellas, C. *et al.* Absence of leptin resistance in platelets from morbidly obese individuals may contribute to the increased thrombosis risk in obesity. *Thromb. Haemost.* **100**, 1123–1129 (2008).
108. Elbatarny, H. S. & Maurice, D. H. Leptin-mediated activation of human platelets: involvement of a leptin receptor and phosphodiesterase 3A-containing cellular signaling complex. *Am. J. Physiol. Endocrinol. Metab.* **289**, E695–E702 (2005).

Acknowledgments

The author's work is funded by the Canadian Institutes of Health Research, Heart & Stroke Foundation of Canada, Canadian Diabetes Association and Korean Ministry of Education Science and Technology. Figures are intended to convey general conclusions from published literature and exceptions may exist.