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**Review Article**

# Novel Molecular Aspects of Ghrelin and Leptin in the Control of Adipobiology and the Cardiovascular System

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**Key Words**

Adipocyte · Adipokines · Appetite · Blood pressure · Cardiometabolic risk · Cardiovascular disorders · Energy balance · Ghrelin · GOAT · Hypertension

**Abstract**

Ghrelin and leptin show opposite effects on energy balance. Ghrelin constitutes a gut hormone that is secreted to the bloodstream in two major forms, acylated and desacyl ghrelin. The isoforms of ghrelin not only promote adiposity by the activation of hypothalamic orexigenic neurons but also directly stimulate the expression of several fat storage-related proteins in adipocytes, including ACC, FAS, LPL and perilipin, thereby stimulating intracytoplasmic lipid accumulation. Moreover, both acylated and desacyl ghrelin reduce TNF-α-induced apoptosis and autophagy in adipocytes, suggesting an anti-inflammatory role of ghrelin in human adipose tissue. On the other hand, leptin is an adipokine with lipolytic effects. In this sense, leptin modulates via PI3K/Akt/mTOR the expression of aquaglyceroporins such as AQP3 and AQP7 that facilitate glycerol efflux from adipocytes in response to the lipolytic stimuli via its translocation from the cytosolic fraction (AQP3) or lipid droplets (AQP7) to the plasma membrane. Ghrelin and leptin also participate in the homeostasis of the cardiovascular system. Ghrelin operates as a cardioprotective factor with increased circulating acylated ghrelin concentrations in patients with left ventricular hypertrophy (LVH) causally related to LV remodeling during the progression to LVH. Additionally, leptin induces vasodilation by inducible NO synthase expression (iNOS) in the vascular wall. In this sense, leptin inhibits the angiotensin II-induced $Ca^{2+}$ increase, contraction and proliferation of VSMC through NO-dependent mechanisms. Together, dysregulation of circulating ghrelin isoforms and leptin resistance associated to obesity, type 2 diabetes, or the metabolic syndrome contribute to cardiometabolic derangements observed in these pathologies.



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## Introduction

Obesity is a serious health problem, becoming one of the leading causes of death and morbidity worldwide [1]. In 2008, 1.5 billion adults were overweight with an estimated 500 million adults worldwide being obese; thus, approximately 65% of the world's population inhabit countries where overweight and obesity kill more people than underweight [1, 2]. Obesity is closely associated to the development of dyslipidemia, insulin resistance, and hypertension that are all well-known risk factors for cardiovascular disease [3]. In this regard, the regional fat distribution is important for the development of the metabolic syndrome and its accompanying cardiovascular complications. Upper body obesity (i.e. visceral or android obesity), as determined by an increased waist circumference and waist-to-hip ratio or elevated visceral or central fat area by image analysis at the lumbosacral level, is associated with increased incidence of metabolic disturbances, elevated risk of cardiovascular disease, and premature death [4, 5]. The adipose tissue constitutes an important source of circulating mediators of inflammation that participate in the mechanisms of cardiovascular injury and atheromateous change [3, 6]. In this sense, adipocytes and adipose tissue-embedded immune cells secrete multiple pro-inflammatory cytokines (TNF-α, IL-6, osteopontin), acute-phase reactants (CRP, SAA), complement factors (adipsin and ASP), prothrombotic molecules (PAI-1, tissue factor), and growth factors (cardiotrophin-1, EGF, FGF). The present review focuses on the participation of leptin and ghrelin, two key hormones in the regulation of energy balance, in the control of adiposity and cardiovascular homeostasis.

## The Components of the Ghrelin System

Ghrelin is a 28-amino acid peptide hormone synthesized by X/A-like cells of the oxyntic glands in the mucosa of the gastric fundus [7]. Although stomach and intestine constitute the two major ghrelin-secreting tissues [8], other tissues express ghrelin, to a lesser extent, including pancreas, kidney, gonads, heart or adipose tissue [9]. The human *GHRL* gene is located on chromosome 3p26-p25 and encodes a polypeptide of 117 amino acids, named preproghrelin, which is proteolytically processed to yield two peptides, ghrelin and obestatin [7, 10]. Two major forms of ghrelin are present in plasma and stomach: acylated ghrelin (form with the *n*-octanoyl modification at Ser3) and desacyl-ghrelin (form without the acylation) [11]. Under physiological conditions, the ratio of acylated ghrelin / desacyl ghrelin ranges in general from 1:3 to 1:4, but this ratio varies under pathological conditions such as chronic atrophic gastritis, chronic renal disease, anorexia nervosa, obesity, type 2 diabetes, or metabolic syndrome [12–16]. Other shorter forms of ghrelin have been described, such as des-Gln14-ghrelin, but their role remains unknown [17]. The acylation of ghrelin is catalyzed by the porcupine-like enzyme ghrelin *O*-acyltransferase (GOAT) in the endoplasmic reticulum (ER) [18, 19].

The growth hormone (GH) secretagogue receptor (GHS-R) is a G protein-coupled receptor that binds ghrelin and acts on the pituitary gland and hypothalamus to stimulate GH release [20]. The human *GHSR* gene maps on chromosome 3q26.31, and two transcripts are produced from the alternative splicing of this gene: GHS-R 1a and 1b. The transcript GHS-R 1a excises an intron, encodes a protein with 366 amino acids with seven transmembrane domains, and is considered the functional ghrelin receptor [20, 21]. The second transcript, GHS-R 1b, retains the intron, encodes a C-terminally truncated isoform of the ghrelin receptor, consisting of 289 amino acids and five transmembrane domains, and does not stimulate GH release. Nevertheless, GHS-R 1b can attenuate the activity of GHS-R 1a by the formation of heterodimers [22]. It has been recently described that the orphan receptor G protein-coupled receptor 83 (GPR83) also forms heterodimers with GHS-R 1a diminishing its activation by acylated ghrelin [23].

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## Leptin and Leptin Receptors

Leptin, the product of the obese (*OB*) gene, is a 16-kDa protein mainly produced and secreted by adipocytes [24]. Etymologically, the name is derived from the Greek word *leptos*, meaning thin, in reference to the anti-obesity effect of the hormone, which initially was believed to be its primary physiological function [25]. The human leptin gene (*LEP*) resides in chromosome 7q31.3 and encodes a protein with a tertiary structure of leptin resembling that of the long-chain helical cytokine family members [26]. Crystallization and nuclear magnetic resonance studies of leptin showed a cytokine-like folding with four antiparallel α-helices, connected by two long crossover links and one short loop arranged in a left-handed helical bundle [27], which forms a two-layer packing. The two cysteine residues of the C-terminus (Cys 96 and 146) form a disulphide bond, which is the key to the biological effects of the protein [28]. The secretion of leptin is proportional to the total amount of body fat, and its circulating concentrations are markedly increased in obesity [29]. In this sense, serum leptin levels range from 1 to 15 ng/ml in non-obese individuals, but reach levels higher than 30 ng/ml in subjects with a BMI ≥ 30 kg/m$^2$ [30]. Moreover, there is a sexual dimorphism in circulating leptin levels with women showing higher leptin concentrations than men [31].

Leptin receptors (OB-R) show structural resemblance to the class I cytokine receptor family, and their ubiquitous distribution underlies the multifunctionality of leptin [32, 33]. At least, six alternative spliced isoforms of the receptor have been identified in rodents, designated OB-Ra, OB-Rb, OB-Rc, OB-Rd, OB-Re and OB-Rf [32], which share a common extracellular domain of over 800 amino acids, a 34-amino acid transmembrane domain and a variable intracellular domain, characteristic for each of the isoforms, with the exception of OB-Re, which lacks the intracellular domain and is a soluble receptor.

## The Role of Leptin and Ghrelin in the Regulation of Body Weight and Adiposity

The hypothalamus integrates changes in adiposity hormones, gastric hormones, and nutrients to control the food intake [34]. There are two subtypes of hypothalamic neurons regulating food intake: i) neurons containing the orexigenic peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP) and, to a lesser extent, galanin and ghrelin; and ii) neurons containing anorexigenic peptides such as proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) and, to a lesser extent, neurotensin. These hypothalamic circuits are regulated by energy status and several circulating hormones, including ghrelin and leptin, that show opposite effects on appetite and adiposity.

### *Anorexigenic and Lipolytic Effect of Leptin*

Leptin reduces food intake and increases energy expenditure to maintain the energy balance [25]. Central administration of leptin results in an activation of several hypothalamic nuclei including the arcuate nucleus (ARC), ventromedial hypothalamus (VMN) and dorsomedial hypothalamus (DMN), all areas involved in the regulation of feeding behavior and energy balance [35]. On binding its hypothalamic receptors, leptin activates anorexigenic neurons containing POMC and CART, decreasing food intake and body weight [35]. Furthermore, leptin increases energy expenditure through the stimulation of sympathetic nerve activity and the turnover of norepinephrine in brown adipose tissue (BAT) [36]. In this sense, leptin plays a crucial role in brown adipogenesis, since leptin-deficient *ob/ob* mice show a 'white-like' appearance of BAT (large unilocular lipid droplets instead of the characteristic small multilocular lipid droplets in brown adipocytes) [37, 38]. Noteworthy, leptin

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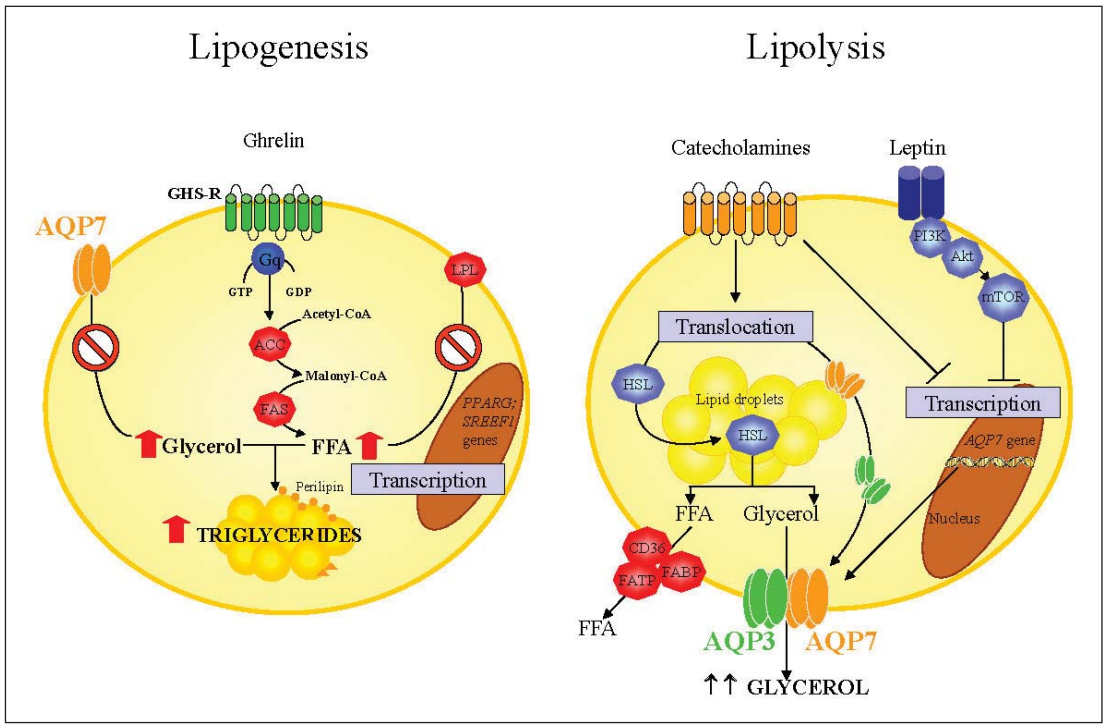


**Fig. 1.** Proposed role of ghrelin and leptin in lipogenesis and lipolysis, respectively. ACC = Acetyl-CoA carboxylase; AQP = aquaporin; CD36 = fatty acid translocase; FFA = free fatty acids; FABP = fatty acid binding protein; FAS = fatty acid synthase; FATP = fatty acid transporter protein; GHS-R = growth hormone secretagogue receptor; HSL = hormone sensitive lipase; LPL = lipoprotein lipase; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol 3-kinase; PPARG = peroxisome proliferator-activated receptor γ gene; SREBF1 = sterol regulatory element-binding factor 1 gene.

also exerts a direct lipolytic effect in white adipose tissue counteracting the tonic inhibition of lipolysis of adenosine deaminase [39].

In circumstances of negative energy balance, such as fasting or exercise, triacylglycerols are hydrolysed to glycerol and free fatty acids (fig. 1) [40, 41]. Lipoprotein (LPL) and fatty acid transporters (FABP, FATP and CD36) facilitate the transport of free fatty acids across the membrane. AQP7 has been considered the unique glycerol channel in the adipose tissue, but AQP3 and AQP9 represent novel additional pathways for the transport of glycerol in human adipocytes [42]. AQP3 and AQP7 show a cytosolic distribution upon the lipid droplets, and they are translocated to the plasma membrane in response to the lipolytic stimulation of isoproterenol, whereas AQP9 is constitutively expressed in the plasma membrane of adipocytes. Lypolityc stimuli, such as catecholamines by the stimulation of β1-, β2- and β3-adrenergic receptors or leptin on binding OB-R and activating PI3K/Akt/mTOR pathway, lead to the translocation of hormone-sensitive lipase (HSL) to the lipid droplets and its activation as well as to a parallel translocation of AQP3 and AQP7 to the plasma membrane to facilitate the glycerol release [42–44]. Interestingly, leptin and catecholamines down-regulate AQP7 expression, suggesting a negative feedback regulation in lipolytic states to restrict glycerol release from adipocytes [42].

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*Orexigenic and Adipogenic Effect of Ghrelin*

Ghrelin plays a major role in the short-term regulation of appetite and long-term regulation of body weight [9]. Circulating concentrations of ghrelin are characterized by a preprandial rise and a postprandial fall, supporting its role in meal initiation in humans [45]. Ghrelin promotes adiposity by increasing food intake through the stimulation of hypothalamic orexigenic neurons expressing NPY, AgRP, and orexin [46, 47]. The orexigenic actions of ghrelin require the activation of hypothalamic sirtuin-1 (SIRT1) / p53, AMP-activated protein kinase (AMPK), and mammalian target of rapamycin (mTOR) pathways, which ultimately increase NPY and AgRP expression in the arcuate nucleus [48–50]. Despite its orexigenic effect, obesity, insulin resistance, type 2 diabetes, and the metabolic syndrome are related to a paradoxical decrease in circulating ghrelin levels [7, 51, 52]. However, these pathologies are associated with a dramatic reduction of plasma desacyl ghrelin concentrations, the most abundant form of the hormone, while plasma levels of acylated ghrelin remain unchanged or increased [19, 53–55].

The adipose tissue also constitutes an important target for the adipogenic actions of ghrelin. All the components of the ghrelin system (ghrelin, GOAT and the receptors of ghrelin gene-related peptides GHS-R 1a and GPR39) are expressed in human adipose tissue [19, 53, 56], suggesting an autocrine/paracrine effect of ghrelin in this tissue. During adipogenesis, ghrelin gene (*GHRL*) expression is increased [57], and ghrelin stimulates the expression of the adipogenic transcription factors peroxisome proliferator-activated receptor γ (PPARγ) and sterol regulatory element-binding transcription factor 1 (SREBF1), and hence, promotes adipocyte differentiation (fig. 1) [53]. In addition, acylated and desacyl ghrelin stimulate the expression of several fat-storage related proteins such as acetyl-CoA carboxylase, fatty acid synthase, LPL or perilipin through central mechanisms [48] and directly acting on human adipocytes [53], thereby stimulating intracellular lipid accumulation. Moreover, ghrelin also has an antilipolytic action [58]. In this sense, acylated and desacyl ghrelin attenuate isoproterenol-induced lipolysis through phosphatidyl-inositol-3 kinase(PI3K)-dependent mechanisms in murine 3T3-L1 cells as well as in isolated rat visceral adipocytes [59]. In this line, the expression of AQP7 in human visceral adipocytes is repressed by acylated and desacyl ghrelin, supporting the view that ghrelin decreases lipolytic capacity and promotes fat cell enlargement [53].

In addition to promote adipogenesis and lipogenesis, ghrelin plays an anti-inflammatory role in the adipose tissue. Acylated and desacyl ghrelin inhibit the activation of caspases and apoptosis induced by TNF-α, and also reduce basal and TNF-α-induced expression of key autophagy-related genes [19]. In this sense, the imbalance of ghrelin isoforms and TNF-α in states of hyperglycemia may contribute to the altered apoptosis and autophagy observed in patients with type 2 diabetes.

## Implication of Leptin and Ghrelin in the Maintenance of Cardiovascular Homeostasis

Obesity has been classified as a major modifiable risk factor for cardiovascular diseases [60]. Excess adiposity is associated with an increase in total blood volume, which, in turn, contributes to an increase in left ventricular (LV) preload and an increase in resting cardiac output (fig. 2) [61, 62]. The increased demand for cardiac output is achieved by an increase in stroke volume, while the heart rate remains comparatively unchanged. The obesity-related increase in stroke volume results from an increase in LV diastolic filling. The increase in circulatory preload and afterload lead to LV dilatation. An elevated cardiac output is common with moderate obesity, but not all obese patients are hypertensive. However, in those subjects

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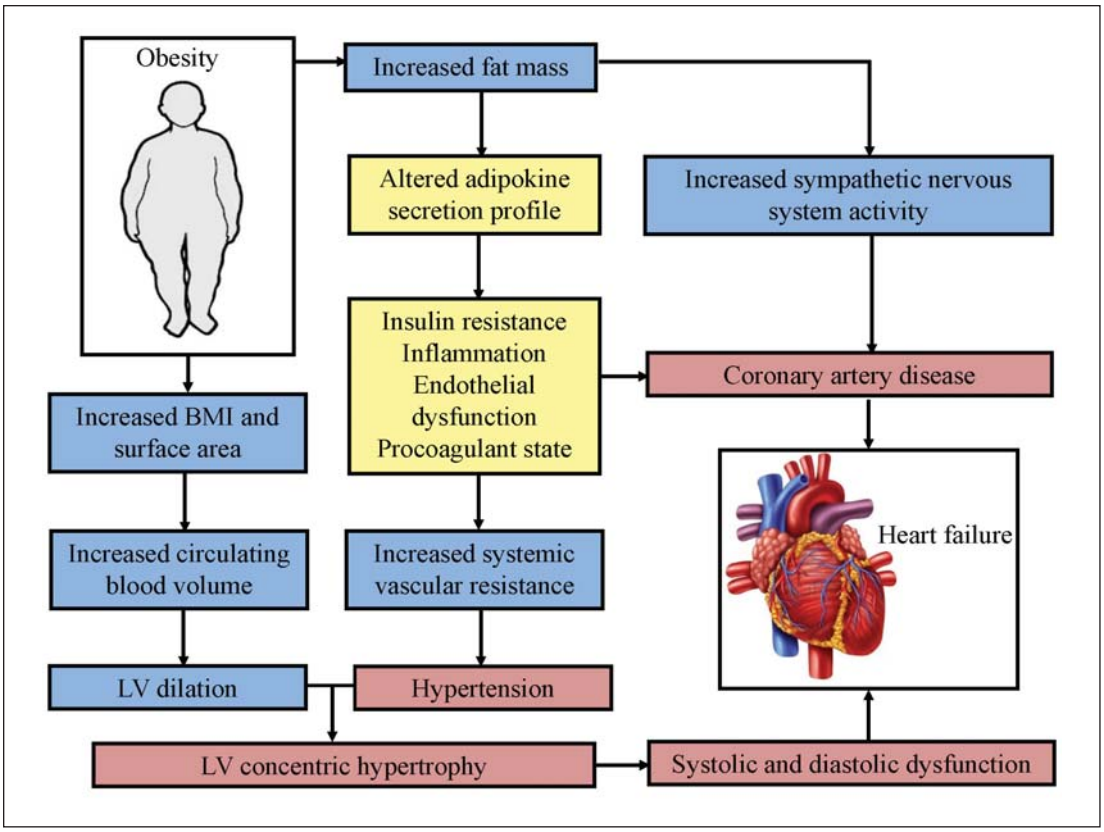


**Fig. 2.** Schematic diagram of obesity-associated cardiovascular alterations leading to heart failure. LV = Left ventricle.

where systemic vascular resistance is increased, the combination of obesity and hypertension results in an increase of LV wall dimensions disproportionate to the chamber radius, and this leads, in turn, to LV concentric hypertrophy. In addition to increased blood pressure values, obese subjects exhibit elevated cardiovascular risk factors which alter vascular function, adding further to the pressure load of the heart [61]. Despite an elevation of cardiac output, obese individuals have been shown to present a depressed 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 a clinically significant risk of heart failure. In this section, we will focus on the role of leptin and ghrelin in the homeostasis of cardiovascular system.

*Vascular Effects of Leptin*

Leptin plays two opposite roles in the regulation of blood pressure by exerting a hypertensive effect due to the sympathoactivation [63] and a vasorelaxant action due to the release of NO in the aorta and coronary arteries and endothelial-derived hyperpolarizing factor in mesenteric arteries (EDHF) [64–67]. On the one hand, intracerebroventricular leptin administration increases blood pressure by increasing sympathetic activity [68]. However, leptin also induces vasodilation by increasing NO bioavailability in peripheral blood vessels through the activation of endothelial NO synthase (eNOS) in endothelial cells [69] and inducible NO synthase (iNOS) in vascular smooth muscle cells (VSMC) [70]. Moreover, leptin inhibits angiotensin II-induced contraction of vascular smooth muscle cells [70, 71]. Leptin attenuates

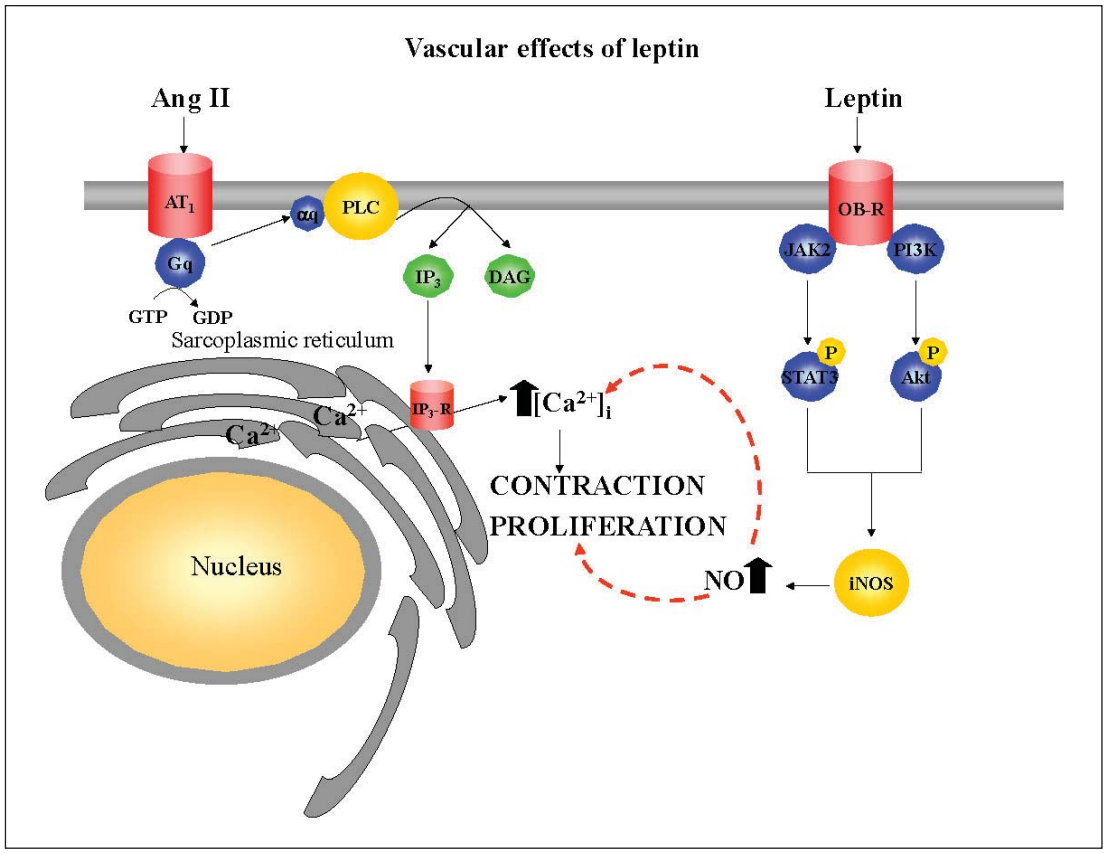


**Fig. 3.** Proposed mechanism for the actions of leptin on vascular smooth muscle cell contraction and proliferation. Ang II = Angiotensin II; AT1 = angiotensin II receptor type 1; DAG = diacylglycerol; JAK = janus kinase; iNOS = inducible nitric oxide synthase; IP3 = inositol triphosphate; NO = nitric oxide; PI3K = phosphatidylinositol 3-kinase; PLC = phospholypase C; STAT = signal transducer and activator of transcription.

angiotensin II-induced release of $Ca^{2+}$ sequestered in the intracellular stores of VSMC that represents the major mechanism used by angiotensin II to induce vasoconstriction (fig. 3). This inhibitory effect of leptin requires the up-regulation of iNOS via the activation of the JAK/STAT and PI3K/Akt pathways [70]. A further mechanism whereby leptin decreases blood pressure is via the activation of natriuresis and diuresis through NO-dependent mechanisms [72].

Increased circulating concentrations of leptin are found in hypertensive animal models [73, 74] and humans [75, 76], suggesting a possible link between hyperleptinemia and hypertension. Interestingly, leptin enhances the expression of the NADPH oxidase isoform 2 (NOX2), and hence, the intracellular accumulation of reactive oxygen species (ROS) in the vascular wall [77, 78]. Spontaneously hypertensive rats, an animal model with features of the metabolic syndrome, show increased NOX2 expression and impaired ability of leptin to inhibit the angiotensin II-induced increase of cytosolic $Ca^{2+}$ and vasoconstriction in VSMC [74, 77, 79]. The hyperleptinemia, increased oxidative stress, and the loss of this anti-contractile effect of leptin suggest that this animal model of hypertension present vascular leptin resistance. In this sense, endothelial dysfunction is characterized by a reduced synthesis and release of endothelium-derived relaxing factors, such as NO and/or an enhanced production of ROS, which scavenge NO within vessels to reduce its biological half-life. Taken together, it could be

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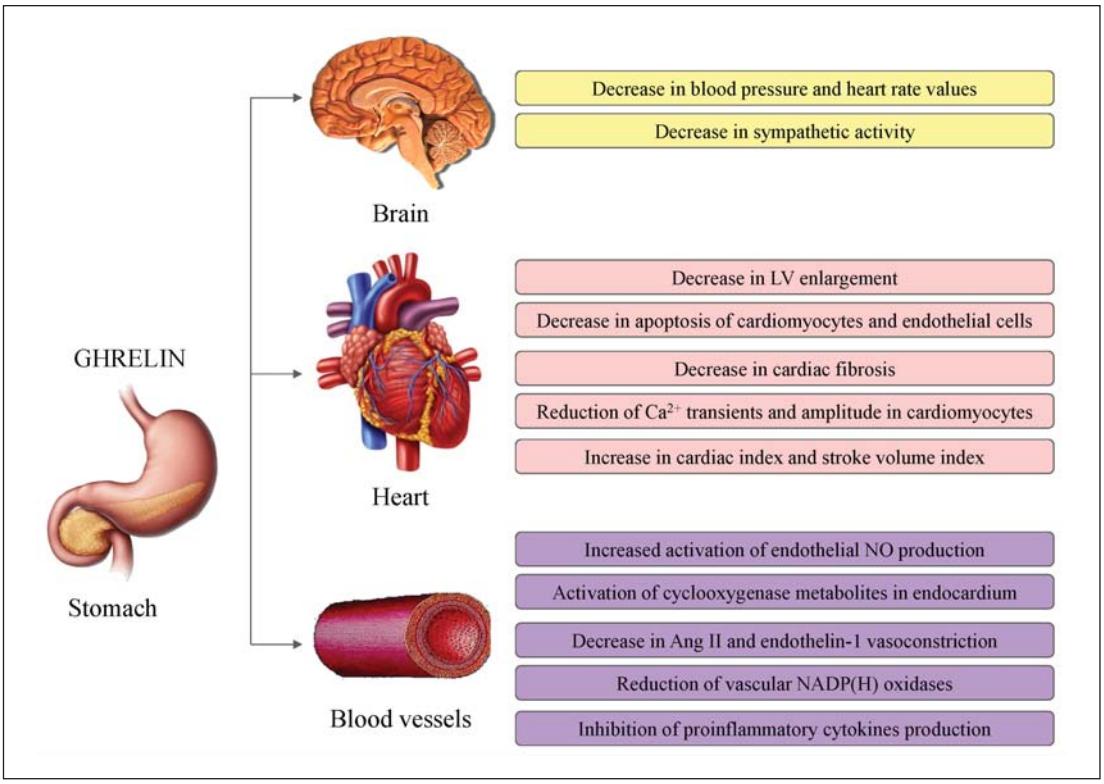


**Fig. 4.** Central and peripheral actions of ghrelin on the control of cardiovascular homeostasis. Ang II = Angiotensin II; LV = left ventricle; NADP(H) = nicotinamide adenine dinucleotide phosphate-oxidase.

speculated that, in the setting of hypertension, the vasodilatory effects of leptin are overridden by the effects of angiotensin II, the increased systemic oxidative stress as well as the excessive sympathoactivation, despite the hyperleptinemia.

Hypertension is associated with structural changes in blood vessels known as vascular remodeling that include an altered VSMC proliferation, hypertrophy, migration, and apoptosis together with an increased extracellular matrix abundance. Angiotensin II constitutes one of the main factors involved in vascular remodeling during the onset of hypertension. Our group has shown that leptin inhibits the proliferative response induced by angiotensin II, via NO-dependent mechanisms (fig. 3) [77]. However, VSMC from hypertensive rats are less responsive to the anti-proliferative effect of leptin, probably due to a reduction in NO bioavailability and increased oxidative stress. Nonetheless, the role of leptin on VSMC proliferation remains unclear, with reports showing either stimulatory [80, 81] or inhibitory [77, 82] effects on this biological process. Thus, the effect of leptin on VSMC proliferation seems to be complex, and further studies are needed to disentangle the potential involvement of leptin in vascular remodeling [83].

*Ghrelin as a Cardioprotective Hormone*

Growing evidence support the role of ghrelin in the control of cardiovascular homeostasis through central and peripheral mechanisms (fig. 4). Intracerebroventricular administration of ghrelin into the nucleus of the solitary tract, a region involved in the regulation of cardiovascular system, induces a decrease in blood pressure and heart rate and also suppresses sympathetic renal activity in experimental animals [84, 85]. In addition, the myocardium

constitutes a source of ghrelin [86], and GHS-R 1a is expressed in cardiomyocytes and other myocardial cells, suggesting an autocrine/paracrine role of ghrelin in the heart [87]. Chronic administration of ghrelin improves cardiac performance in rats and humans with chronic heart failure (CHF), as indicated by increases in cardiac output, LV fractional shortening, and ejection fraction [88–90]. Moreover, a single dose of ghrelin after myocardial infarction prevents an increase in cardiac sympathetic nerve activity and reduces the high mortality rate associated with this pathology [91]. In this line, *Ghrl* knockout mice exhibit excessive sympathoactivation, impaired LV function, early cardiac remodeling, and higher mortality after myocardial infarction, a fact that further suggests the crucial role of ghrelin in the maintenance of heart function [88].

The mechanisms underlying the cardioprotective actions of ghrelin include: i) negative inotropism by activating the release of cyclooxygenase metabolites in endocardial endothelium and by reducing the amplitude and rising rate of cytosolic $Ca^{2+}$ transients in cardiomyocytes [92, 93]; ii) vasodilation by inducing endothelial NO release through PI3K-dependent mechanisms as well as by reducing endothelin-1, angiotensin II, and vascular NADP(H) oxidases activities [94–96]; iii) inhibition of apoptosis in cardiomyocytes and endothelial cells through activation of mitogen-activated protein kinase p42/44 (ERK1/2) and PI3K/Akt signaling pathways and by inhibiting the activation of the endoplasmic reticulum stress pathway [97, 98]; and iv) reduction of endothelial and cardiac inflammation through the inhibition of pro-inflammatory cytokine production, mononuclear cell binding and nuclear factor-κB (NF-κB) in endothelial cells, as well as through the suppression of myocardial levels of TNF-α and IL-6 [99, 100].

Total ghrelin levels are decreased in several cardiovascular disorders, such as pregnancy-induced hypertension, essential hypertension, atherosclerosis, coronary heart disease, and CHF [101–104]. However, the specific role of ghrelin isoforms in these pathologies has not been completely disentangled. In this regard, the metabolic syndrome, an important risk factor for cardiovascular disease incidence and mortality, is related to higher plasma acylated ghrelin and lower concentrations of desacyl ghrelin [54]. Interestingly, acylated ghrelin is positively associated with LV mass and higher blood pressure in patients with the metabolic syndrome, suggesting a role of this isoform of the hormone in the progression of LV hypertrophy and other cardiovascular complications in these patients.

## Conclusions

Weight gain is accompanied by progressive physiological changes in cardiovascular function that can lead to heart failure [61]. It is well established that a modest weight loss ranging from 5 to 10% of the initial body weight by means of diet, exercise, or bariatric surgery results in an improvement of obesity-associated cardiometabolic disturbances [3]. Epidemiological and interventional studies have shown the beneficial effects of weight loss on cardiovascular mortality and morbidity due to favorable implications on LV hypertrophy as well as beneficial effects on coronary risk [105].

Obesity is associated with hyperleptinemia, an imbalance of ghrelin isoforms as well as with an impairment of transduction signal in effector organs, suggesting the pivotal role of leptin and ghrelin in the control of adiposity and cardiovascular homeostasis. Sleeve gastrectomy, an effective bariatric procedure for the treatment of morbid obesity, is associated with a reduction of blood pressure, but not heart rate, in genetically obese Zucker *fa/fa* rats beyond weight loss [106]. The same was true in an animal model of diet-induced obesity that showed a further reduction of heart rate values without loss of cardiac mass [107]. Interestingly, sleeve gastrectomy is associated with a dramatic reduction of circulating

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leptin and ghrelin concentrations. It seems plausible that the decrease in leptin and ghrelin concentrations together with the improved intracellular signaling in the adipose tissue and cardiovascular system play a key role in the reduction of obesity-associated cardiometabolic alterations. In line with this observation, a recent study has shown that the offspring of rabbits exposed to high-fat diet during pregnancy exhibited an increase in sympathetic renal activity and blood pressure due to an altered central hypothalamic sensitivity to ghrelin and leptin [108]. Given the current prevalence of obesity, better understanding the underlying mechanisms that relate fat mass to cardiovascular health induced by leptin and ghrelin is of paramount importance, since obesity is a major modifiable contributor to cardiovascular disease.

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## Disclosure Statement

The author declares no conflict of interests.

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