We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Chapter

Mineralocorticoid Receptor and Leptin: A Dangerous Liaison in the Obese Heart

Gema Marin-Royo, María Luaces, Victoria Cachofeiro and Ernesto Martínez-Martínez

Abstract

Multiple factors have been proposed as being responsible for cardiac damage in the context of obesity, including aldosterone/mineralocorticoid receptor and leptin. Aldosterone exerts proinflammatory, prooxidant and profibrotic actions, which can play a key role in the development of cardiac damage associated with different pathologies, through binding of mineralocorticoid receptor (MR). Moreover, its pharmacological blockade has demonstrated to improve these situations. Different studies have demonstrated that aldosterone is inappropriately elevated in obesity and MR antagonism improves left ventricle function and reduces circulating procollagen levels in patients with obesity without other comorbidities. Leptin is locally produced in the myocardium and its production is up-regulated in obesity. This adipokine is a proinflammatory, prooxidant and profibrotic factor that can participate in the cardiac damage associated with obesity. Interactions among leptin and aldosterone have previously been reported in different scenarios and at different levels, supporting a link between leptin and MR and that could result in the potentiation of the cardiac damage associated with obesity. Therefore, the aim of this review is to discuss whether MR activation can mediate the deleterious effects of leptin in the heart in the context of obesity, as well as the potential mechanisms involved in this process.

Keywords: leptin, mineralocorticoid receptor, fibrosis, heart, oxidative stress

1. Cardiac effects of obesity

Obesity has become a global problem of the first magnitude worldwide and is associated with an increase in total mortality, especially that of cardiovascular origin [1]. Obesity is an exaggeration of normal adiposity and plays a central role in the pathophysiology of various diseases such as type 2 diabetes mellitus, cardiovascular disease, stroke, hypertension, and dyslipidemia [2]. Obesity is associated with several structural and function alterations in the heart which are characterized by cardiac hypertrophy and left ventricle systolic and diastolic dysfunction that contribute to the development of heart failure [3]. There have been reported changes in left ventricle geometry in obese individuals, with these being more prevalent in an eccentric pattern defined by an increase in left ventricle mass but not in relative parietal thickness [4]. This cardiac hypertrophy could be a consequence of higher

metabolic demand required by obese individuals, as well as increased cardiac output which is associated with higher ventricular filling and which promotes ventricular dilatation and, in consequence, an enlargement of myocardial mass [5]. It is well known that left ventricular hypertrophy is a risk factor for heart failure development [6]. Diastolic dysfunction is the main functional alteration observed in obese patients [7]. Ventricular hypertrophy along with an increase in blood flow and circulating volume predisposes to diastolic dysfunction observed in obese patients [4]. Pascual et al. reported subclinical left ventricular diastolic dysfunction in all degrees of obesity (mildly, moderate, and severely obese patients) [8]. Another study reported that the severity of the diastolic dysfunction observed in obesity increases proportionally with the body mass index [9]. Conflicting results have been found [8, 10–14] with regard to systolic function in obese individuals. These contradictory effects on systolic function could be consequence of the presence or not of comorbidities frequently associated with obesity (hypertension, metabolic disorders, and coronary artery disease) which can also have an impact on cardiac function. Several studies have postulated that perivascular and interstitial fibrosis could contribute to the cardiac dysfunction, especially diastolic one, observed in obesity [15]. Cardiac fibrosis is characterized by increased deposit of extracellular matrix (ECM) proteins in the myocardium. This is a dynamic process regulated by the balance between the synthesis and degradation of the ECM proteins within the heart. Collagen, especially collagen type I, is the main protein involved in fibrotic process, and metalloproteinases (MMPs) are the enzymes involved in ECM protein degradation. It has been described that obese patients present elevated serum levels of collagen peptides and are associated with indices of insulin resistance and with diastolic dysfunction [16, 17]. Moreover, the reduction in body mass index after bariatric surgery is not always accompanied by the normalization of diastolic function suggesting myocardial damage probably due to the accumulation of ECM [4].

Several mechanisms and factors have been proposed for the structural and functional changes that occur in the obese heart, such as, the effects of aldosterone, through mineralocorticoid receptor (MR) binding, and leptin, two hormones whose levels are increased in the context of obesity. Aldosterone/MR and leptin promote cardiac damage through its prooxidant and proinflammatory effects which can trigger an excessive ECM accumulation, promoting fibrogenic and hypertrophic responses and functional alterations [18–20]. We herein review the MR and leptin effects at cardiac level with special focus on the context of obesity as well as the interaction of aldosterone and leptin and its role in the development of cardiac remodeling.

2. Cardiac effects of mineralocorticoid receptor

Aldosterone is the main mineralocorticoid hormone, which plays an important role in the pathophysiology of cardiovascular disease through its binding to MR, which resides in the cytosol and is translocated to the nucleus after ligand binding, thereby promoting gene transcription [21]. Besides the hypertensive and the renal effects of aldosterone, chronic hyperaldosteronism promotes cardiovascular complications, including left ventricular hypertrophy, myocardial infarction, and atrial fibrillation [22]. The deleterious effects of aldosterone have traditionally been considered over the years due to its effects on sodium/water retention and its effects on blood pressure. However, its extrarenal effects through MR activation in non-epithelial cells of the cardiovascular system have been confirmed in recent years [23]. Several clinical studies have demonstrated that the activation of MR plays an important role in mild to severe heart failure [24–26]. MR blockade through MR antagonists (MRA) reduces morbidity and mortality in heart failure patients. MRA treatment

has demonstrated beneficial effects at cardiac level even in the absence of aldosterone level modifications [24–26]. In accordance with these observations, the effects of MR by genetic modulation in different cell types have been demonstrated. Specifically, MR overexpression in cardiomyocytes leads to cardiac arrhythmias in mice in the absence of changes in aldosterone levels [27], and this effect is accompanied by severe coronary endothelial dysfunction due at least in part to an increase in oxidative stress [28]. In addition, mice with MR genetic deletion in cardiomyocytes are resistant to developing cardiac fibrosis induced by deoxycorticosterone/salt (DOCA-salt) and do not show inflammatory cell infiltration after 8 weeks of treatment [29]. In another animal model of cardiac disease, Fraccarollo et al. have demonstrated that MR deletion in cardiomyocytes improved infarct healing, cardiac function, cardiac fibrosis, and mitochondrial superoxide anion production after myocardial infarction, which confirms the role of MR activation in cardiac cells in cardiac pathophysiology [30]. Similar beneficial effects on cardiac remodeling, hypertrophy, and profibrotic and proinflammatory markers have been observed in endothelial [31, 32] or macrophage [33] MR inactivation after DOCA-salt mineralocorticoid challenge and also in vascular smooth muscle MR inactivation in myocardial infarction [34].

In the context of obesity, clinical and experimental studies have demonstrated that aldosterone production is increased in obesity and is correlated with white adipose tissue mass [35–37]. In addition, weight loss in obese individuals is accompanied by a reduction in aldosterone levels [38]. Aldosterone is primarily synthesized in the outer layer of the adrenal cortex. However, it has been demonstrated that adipose tissue possesses the machinery necessary to produce aldosterone, which can act in an autocrine or paracrine manner [39]. Activation of renin-angiotensin-aldosterone system has been reported in animal models of obesity [20, 40, 41]. Endothelial-specific MR deletion in female mice was able to prevent the diastolic dysfunction induced by high-fat diet [42]. This improvement was accompanied by a reduction in cardiac fibrosis, ECM protein deposition, cardiac inflammation, and oxidative stress as well as an improvement in insulin metabolic signaling [42]. These results were confirmed by the same research group where the administration of the MRA spironolactone reproduced the same results [43] in female mice fed with a high-fat diet as well as prevented the development of arterial stiffening in the animals [44]. In agreement with these findings, a randomized controlled clinical study has shown that aldosterone blockade with spironolactone for 6 months improved left ventricular function and reduced circulating procollagen peptide levels in obese patients without other comorbidities [45]. The addition of spironolactone to the standard treatment (angiotensin II inhibitors) was also able to improve left ventricle dysfunction and collagen turnover in patients with metabolic syndrome [46]. In a recent study, we have demonstrated that galectin-3, a lectin upregulated by MR activation, is increased in obese patients and its levels were associated with diastolic function [17]. In addition, pharmacological blockade of galectin-3 with an activity inhibitor blunted the cardiovascular remodeling and inflammation in obese male rats [17]. Another study in obese rats showed that the administration of spironolactone normalized cardiac diastolic function and reduced cardiac fibrosis [47]. The studies performed in the context of obesity overall show the implication of MR in cardiac damage and the beneficial consequences of the use of MRA in the treatment of obesity-related cardiovascular dysfunction.

3. Cardiac effects of leptin

Leptin is the product of the *ob* gene that circulates in proportion to body fat [48]. This hormone is considered critical for informing the central nervous system

about the status of energy reserves and control satiety [49]. It is thought that obese people are leptin-resistant due to the lack of satiation observed. However, this leptin resistance does not occur in peripheral tissues, including the cardiovascular system, where leptin promotes several actions in obesity [50]. Leptin is mainly produced by adipose tissue, but it is also produced in different tissues, including the heart [48]. Plasma leptin levels have been considered to be an independent predictor of coronary heart disease [51] and a risk factor for myocardial infarction [52] and coronary atherosclerosis [53]. During obesity there is an increase in systemic leptin levels, as well as in the heart where it is locally produced [54]. Leptin acts via transmembrane receptors which are the product of *db* gene [55]. Genetic deletion of *ob* or *db* genes promotes obese animals, which have been used in conjunction with diet-induced obese animals in order to study the role of leptin in the cardiovascular system [56–58]. Several mechanisms have demonstrated the pathogenic role of leptin at cardiac level. Leptin receptor-deficient obese Zucker rats have been a studied animal model of hyperglycemia and diabetes [59], cardiac lipotoxicity [60], and diastolic cardiac dysfunction [61] as well. In accordance with this metabolic alterations, it has been demonstrated that leptin increased fatty acid uptake in HL-1 cells leading to intracellular lipid accumulation [62] being one possible mechanism involved in cardiac lipotoxicity that can facilitate the development of heart failure [63].

Concerning structural modifications observed in obesity, clinical data have shown a positive correlation between plasma leptin levels with left ventricular hypertrophy [64]. Infusion of leptin in myocardial infarction mice increased left ventricle diameter as compared with animals without leptin infusion [65]. In vitro data show the direct hypertrophic effects of leptin inducing elongation of cardiac myocytes via the activation of JAK/STAT pathway [65]. Despite the well-established hypertrophic effects of leptin, there is one report that documented contradictory effects. *Ob/ob* mice have shown cardiac hypertrophy which is reverted after leptin repletion [66]. It is documented that oxidative stress plays an important role in the development of cardiac hypertrophy [67]. Leptin levels are correlated with superoxide anion levels in peripheral blood mononuclear cells from obese patients after adjusting for age and sex [68]. In this context, leptin produced an increase in reactive oxygen species (ROS) accumulation in a dose- and time-dependent manner in endothelial cells, accompanied by an activation of the JNK pathway [69]. Similar results have been observed in vascular smooth muscle cells [70] and in cardiac fibroblasts [54]. In addition, an antioxidant treatment in vascular and cardiac cells was able to prevent the increase in collagen production induced by leptin [54, 70], showing the role of oxidative stress in fibrogenic responses. Experimental studies have shown that leptin administration in *ob/ob* mice increased myocardial collagen deposition, thus confirming its profibrotic effects [71]. Complementary techniques revealed cardiac interstitial fibrosis in *db/db* mice [72] and in Zucker rats [73], and it is associated with diastolic dysfunction. Multiple mechanisms have been suggested as being responsible for the interstitial fibrosis observed in these animals, including metabolic alterations and the activation of renin-angiotensin-aldosterone system. However, the potential role of leptin in the aldosterone/MR activation observed in these animals is likely acting through mechanisms other than leptin, since both *db/db* mice and Zucker rats have impaired leptin signaling. These potential mechanisms could include angiotensin II, oxidative stress, or metabolic alterations [47, 74–76].

In a recent study, we have demonstrated that leptin enhances lysyl oxidase (LOX) protein levels in cardiac fibroblasts [77]. LOX is an ECM enzyme that catalyzes the cross-linking of collagen fibers [78]. The pharmacological inhibition

of LOX is able to prevent the increase in collagen production induced by leptin in cardiac and vascular cells as well as the cardiovascular fibrosis associated with obesity [77]. In addition, we have observed that leptin increased the aldosterone downstream product, galectin-3, protein levels in cardiac fibroblasts, which at the same time mediates the fibrotic effect of leptin [54] supporting the possible relationship between leptin and MR.

Another mechanism involved in cardiac injury in obesity is the inflammation [79]. Leptin can be considered to be an inflammatory cytokine itself [80] but also promotes monocyte recruitment [81] and macrophage foam cell formation [82] and promotes the secretion of another inflammatory cytokines [83]. The present knowledge of the mechanisms triggered by leptin has established the implication of this adipokine in the deleterious consequences of obesity in the cardiovascular system.

4. Leptin-aldosterone/MR axis

Leptin is a major stimulus to the production of aldosterone in obesity [41, 84] and may be responsible for the excessive MR signaling that is the hallmark of obesity-related heart failure [85, 86]. This thus supports a cross talk between leptin and MR, which can have deleterious consequences in the context of obesity including sodium balance. In this regard, visceral adiposity leads to positive sodium balance through the leptin receptor, which can cause sodium retention [87] through different mechanisms which include a direct action on the renal tubules, an increase in renal sympathetic nerve traffic [88, 89], and a direct stimulation of renin-angiotensin-aldosterone system [90, 91].

Obesity is associated with dysfunctional adipose tissue, which is characterized by the increase in the synthesis of different cytokines as well as leptin. In addition to leptin which is able to stimulate aldosterone synthesis and therefore active MR, whether other adipokines, such as, tumor necrosis factor-α, are able to increase aldosterone is not totally established in the literature since a variety of results have been reported [41, 92].

Leptin infusion in obese and lean mice promotes an increase in aldosterone plasma levels suggesting a relationship between both hormones [93]. Confirming these results, Huby et al. have demonstrated that there is an increase in aldosterone production in an animal model of leptin hypersensitivity due to an increase in *CYP11B2* (aldosterone synthase) expression [90]. The authors showed in the same study that this increase in aldosterone and CYP11B2 is absent in three different transgenic models of leptin activity deletion [90]. In fact, leptin receptors are colocalized with *CYP11B2* in human adrenal cells. In addition, the administration of the leptin receptor antagonist prevented the rise in aldosterone plasma levels observed in the leptin hypersensitivity animal model as well as in obese mice [94]. These data taken together demonstrate that aldosterone production induced by leptin is dependent on leptin signaling rather than on the increase in body weight. However, there are several discrepancies in this suggestion [95]. The mechanisms involved in aldosterone production induced by leptin are still unclear, although it has been proposed to be a calcium-dependent process. In human adrenocortical carcinoma cells, leptin increased calcium activity as well as *CYP11B2* aldosterone production. When intracellular calcium is chelated, leptin-treated cells do not show the increase in *CYP11B2* promoter activity [90].

Female mice infused with leptin presented reduced endothelium-dependent relaxation, which was prevented by spironolactone treatment—this demonstrates

that leptin induces endothelial dysfunction via MR [90]. In the same study, the authors showed that leptin administration for 7 days induced an increase in mRNA levels in profibrotic markers at cardiac level, which was blunted by treatment with spironolactone. This effect is independent of body weight since obese transgenic mice (*ob/ob*) only presented the increase in the profibrotic markers when they were treated with leptin [90]. The transgenic background could explain this effect since *ob/ob* mice are deficient in leptin, suggesting that leptin induced cardiac fibrosis through MR.

As it has been mentioned above, circulating leptin levels are increased in obesity but also are increased locally at cardiac level [54]. In previous studies, we have demonstrated that leptin participates in collagen I production through its prooxidant effects and suggests its possible role in the cardiac fibrosis associated with obesity [54]. Considering that mitochondria is the main source of ROS production, we explored in a recent study the possible role of mitochondrial oxidative stress in cardiac alterations in obesity [40]. For this purpose, we used a normotensive model of diet-induced obesity in rats treated with either MitoTEMPO (a mitochondrial ROS scavenger) or vehicle. The mitochondrial antioxidant was able to prevent the increase in superoxide anion production, as well as the cardiac hypertrophy and fibrosis in obese rats, thus showing the role of mitochondrial ROS in these alterations [40]. Interestingly, these effects of MitoTEMPO were accompanied by a reduction in leptin and aldosterone plasma levels in obese rats, suggesting a possible cross talk between both hormones. For this reason, we explored this possible interaction in cardiac myofibroblasts. In these cells, leptin increased *CYP11B2* mRNA levels (**Figure 1A**) which was accompanied by an increase in the production of aldosterone in a dose- and time-dependent manner (**Figure 1B** and **C**).

In addition, leptin increased ECM proteins, profibrotic mediators, and the production of superoxide anion at total and mitochondrial level through the activation of Akt and ERK1/ERK2 pathways [40]. The pharmacological blockade of MR through pretreatment of the cells with eplerenone was able to prevent all these alterations induced by leptin in the cardiac cells, thus showing the cross talk between MR and leptin. The results taken together show the possible role of leptin in cardiac fibrosis in the context of obesity through MR-dependent mechanisms (**Figure 2**) [40].
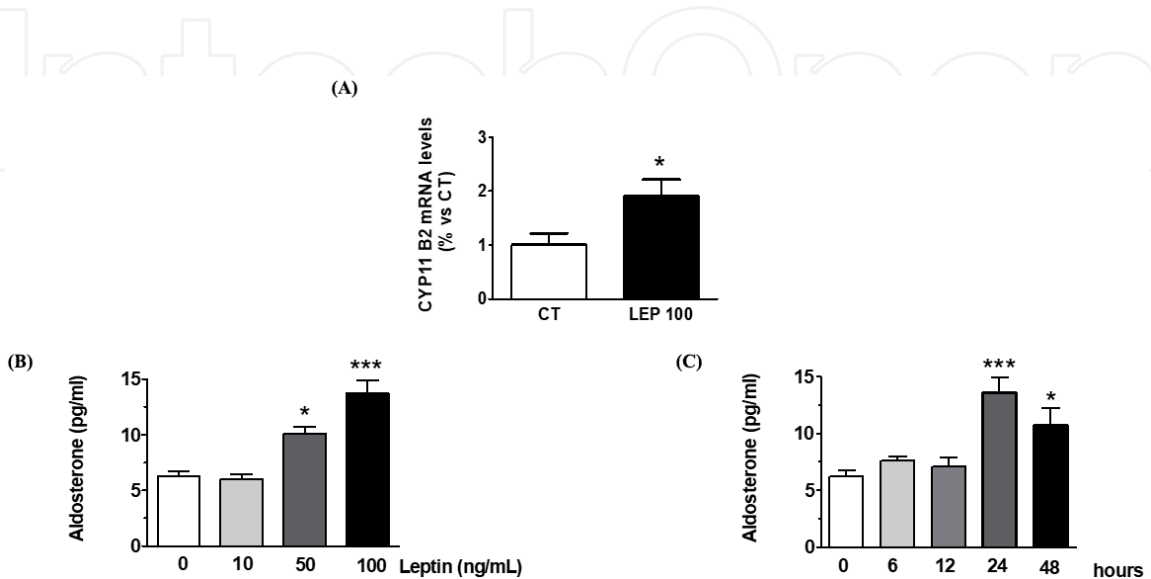
Figure 1.
*(A) Effects of leptin (100 ng/mL) on CYP11B2 mRNA levels at 24 hours of stimulation. (B) Dose-response and (C) time-course of leptin on aldosterone secretion in human cardiac fibroblasts. *$p < 0.05$; ***$p < 0.001$ vs. control.*
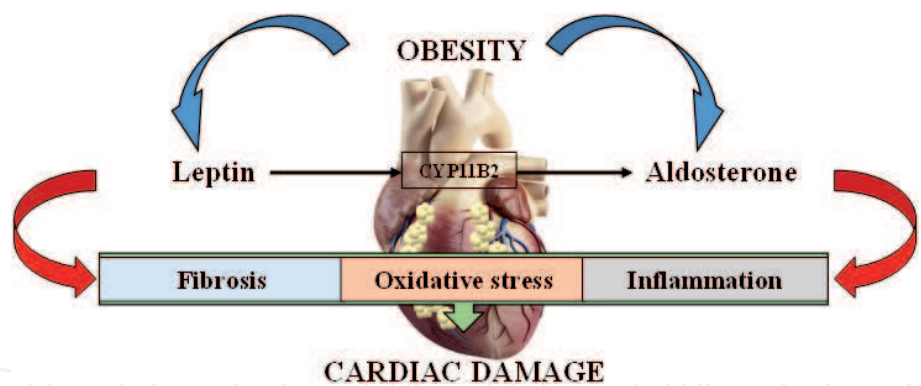
Figure 2.
Scheme illustrating the cross talk between leptin and aldosterone and different mechanisms involved in the cardiac damage associated with obesity.

Acknowledgements

Author details

Gema Marin-Royo[1], María Luaces[2], Victoria Cachofeiro[1]*
and Ernesto Martínez-Martínez[1]

1 Departamento de Fisiología, Facultad de Medicina, Universidad Complutense de Madrid and Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

2 Servicio de Cardiología, Instituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain

*Address all correspondence to: vcara@med.ucm.es

IntechOpen

References

[1] Kenchaiah S et al. Obesity and the risk of heart failure. The New England Journal of Medicine. 2002;**347**(5):305-313

[2] Pischon T et al. General and abdominal adiposity and risk of death in Europe. The New England Journal of Medicine. 2008;**359**(20):2105-2120

[3] Alpert MA, Karthikeyan K, Abdullah O, Ghadban R. Obesity and cardiac remodeling in adults: Mechanisms and clinical implications. Progress in Cardiovascular Diseases. 2018;**61**(2):114-123

[4] Luaces M et al. Anatomical and functional alterations of the heart in morbid obesity. Changes after bariatric surgery. Revista Española de Cardiología (English Edition). 2012;**65**(1):14-21

[5] Ku CS, Lin SL, Wang DJ, Chang SK, Lee WJ. Left ventricular filling in young normotensive obese adults. The American Journal of Cardiology. 1994;**73**(8):613-615

[6] Kannel WB et al. Profile for estimating risk of heart failure. Archives of Internal Medicine. 1999;**159**(11):1197-1204

[7] Alpert MA, Omran J, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Current Obesity Reports. 2016;**5**(4):424-434

[8] Pascual M et al. Effects of isolated obesity on systolic and diastolic left ventricular function. Heart. 2003;**89**(10):1152-1156

[9] Alpert MA et al. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. The American Journal of Cardiology. 1997;**80**(6):736-740

[10] Herszkowicz N et al. Contribution of Doppler echocardiography to the evaluation of systolic and diastolic function of obese women versus a control group. Arquivos Brasileiros de Cardiologia. 2001;**76**(3):189-196

[11] Willens HJ et al. Tissue Doppler imaging of the right and left ventricle in severe obesity (body mass index >35 kg/m^2). The American Journal of Cardiology. 2004;**94**(8):1087-1090

[12] Otto ME et al. Comparison of right and left ventricular function in obese and nonobese men. The American Journal of Cardiology. 2004;**93**(12):1569-1572

[13] Tumuklu MM, Etikan I, Kisacik B, Kayikcioglu M. Effect of obesity on left ventricular structure and myocardial systolic function: Assessment by tissue Doppler imaging and strain/strain rate imaging. Echocardiography. 2007;**24**(8):802-809

[14] Orhan AL et al. Effects of isolated obesity on left and right ventricular function: A tissue Doppler and strain rate imaging study. Echocardiography. 2010;**27**(3):236-243

[15] Wong C, Marwick TH. Obesity cardiomyopathy: Pathogenesis and pathophysiology. Nature Clinical Practice. Cardiovascular Medicine. 2007;**4**(8):436-443

[16] Quilliot D et al. Myocardial collagen turnover in normotensive obese patients: Relation to insulin resistance. International Journal of Obesity. 2005;**29**(11):1321-1328

[17] Martinez-Martinez E et al. Galectin-3 participates in cardiovascular remodeling associated with obesity. Hypertension. 2015;**66**(5):961-969

[18] Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiological Reviews. 2008;**88**(2):389-419

[19] Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. The Journal of Clinical Investigation. 2011;**121**(6):2111-2117

[20] Cavalera M, Wang J, Frangogiannis NG. Obesity, metabolic dysfunction, and cardiac fibrosis: Pathophysiological pathways, molecular mechanisms, and therapeutic opportunities. Translational Research. 2014;**164**(4):323-335

[21] Jaisser F, Farman N. Emerging roles of the mineralocorticoid receptor in pathology: Toward new paradigms in clinical pharmacology. Pharmacological Reviews. 2016;**68**(1):49-75

[22] Briet M, Schiffrin EL. Aldosterone: Effects on the kidney and cardiovascular system. Nature Reviews. Nephrology. 2010;**6**(5):261-273

[23] Fiebeler A, Muller DN, Shagdarsuren E, Luft FC. Aldosterone, mineralocorticoid receptors, and vascular inflammation. Current Opinion in Nephrology and Hypertension. 2007;**16**(2):134-142

[24] Pitt B et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. New England Journal of Medicine. 1999;**341**(10):709-717

[25] Pitt B et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. The New England Journal of Medicine. 2003;**348**(14):1309-1321

[26] Zannad F et al. Eplerenone in patients with systolic heart failure and mild symptoms. The New England Journal of Medicine. 2011;**364**(1):11-21

[27] Ouvrard-Pascaud A et al. Conditional mineralocorticoid receptor expression in the heart leads to life-threatening arrhythmias. Circulation. 2005;**111**(23):3025-3033

[28] Favre J et al. Coronary endothelial dysfunction after cardiomyocyte-specific mineralocorticoid receptor overexpression. American Journal of Physiology. Heart and Circulatory Physiology. 2011;**300**(6):H2035-H2043

[29] Rickard AJ et al. Cardiomyocyte mineralocorticoid receptors are essential for deoxycorticosterone/salt-mediated inflammation and cardiac fibrosis. Hypertension. 2012;**60**(6):1443-1450

[30] Fraccarollo D et al. Deletion of cardiomyocyte mineralocorticoid receptor ameliorates adverse remodeling after myocardial infarction. Circulation. 2011;**123**(4):400-408

[31] Rickard AJ et al. Endothelial cell mineralocorticoid receptors regulate deoxycorticosterone/salt-mediated cardiac remodeling and vascular reactivity but not blood pressure. Hypertension. 2014;**63**(5):1033-1040

[32] Lother A et al. Deoxycorticosterone acetate/salt-induced cardiac but not renal injury is mediated by endothelial mineralocorticoid receptors independently from blood pressure. Hypertension. 2016;**67**(1):130-138

[33] Rickard AJ et al. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. Hypertension. 2009;**54**(3):537-543

[34] Gueret A et al. Vascular smooth muscle mineralocorticoid receptor contributes to coronary and left

ventricular dysfunction after myocardial infarction. Hypertension. 2016;**67**(4):717-723

[35] Goodfriend TL, Egan BM, Kelley DE. Plasma aldosterone, plasma lipoproteins, obesity and insulin resistance in humans. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 1999;**60**(5-6):401-405

[36] Harada E et al. Increased urinary aldosterone excretion is associated with subcutaneous not visceral, adipose tissue area in obese individuals: A possible manifestation of dysfunctional subcutaneous adipose tissue. Clinical Endocrinology. 2013;**79**(4):510-516

[37] Silva MA et al. Mineralocorticoid receptor blockade prevents vascular remodelling in a rodent model of type 2 diabetes mellitus. Clinical Science (London, England). 2015;**129**(7):533-545

[38] Calhoun DA, Sharma K. The role of aldosteronism in causing obesity-related cardiovascular risk. Cardiology Clinics. 2010;**28**(3):517-527

[39] Briones AM et al. Adipocytes produce aldosterone through calcineurin-dependent signaling pathways: Implications in diabetes mellitus-associated obesity and vascular dysfunction. Hypertension. 2012;**59**(5):1069-1078

[40] Gutierrez-Tenorio J et al. The role of oxidative stress in the crosstalk between leptin and mineralocorticoid receptor in the cardiac fibrosis associated with obesity. Scientific Reports. 2017;**7**(1):16802

[41] Xie D, Bollag WB. Obesity, hypertension and aldosterone: Is leptin the link? The Journal of Endocrinology. 2016;**230**(1):F7-F11

[42] Jia G et al. Endothelial mineralocorticoid receptor deletion prevents diet-induced cardiac diastolic dysfunction in females. Hypertension. 2015;**66**(6):1159-1167

[43] Bostick B et al. Mineralocorticoid receptor blockade prevents Western diet-induced diastolic dysfunction in female mice. American Journal of Physiology. Heart and Circulatory Physiology. 2015;**308**(9):H1126-H1135

[44] DeMarco VG et al. Low-dose mineralocorticoid receptor blockade prevents western diet-induced arterial stiffening in female mice. Hypertension. 2015;**66**(1):99-107

[45] Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, Marwick TH. Fibrosis and cardiac function in obesity: A randomised controlled trial of aldosterone blockade. Heart. 2013;**99**(5):320-326

[46] Kosmala W et al. A randomized study of the beneficial effects of aldosterone antagonism on LV function, structure, and fibrosis markers in metabolic syndrome. JACC: Cardiovascular Imaging. 2011;**4**(12):1239-1249

[47] Bender SB et al. Mineralocorticoid receptor antagonism treats obesity-associated cardiac diastolic dysfunction. Hypertension. 2015;**65**(5):1082-1088

[48] Pan WW, Myers MG Jr. Leptin and the maintenance of elevated body weight. Nature Reviews. Neuroscience. 2018;**19**(2):95-105

[49] Rahmouni K. Leptin-induced sympathetic nerve activation: Signaling mechanisms and cardiovascular consequences in obesity. Current Hypertension Reviews. 2010;**6**(2):104-209

[50] Enriori PJ, Evans AE, Sinnayah P, Cowley MA. Leptin resistance and obesity. Obesity (Silver Spring). 2006;**14**(Suppl 5):254S-258S

[51] Wallace AM et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation. 2001;**104**(25):3052-3056

[52] Soderberg S et al. Leptin is associated with increased risk of myocardial infarction. Journal of Internal Medicine. 1999;**246**(4):409-418

[53] Wolk R et al. Plasma leptin and prognosis in patients with established coronary atherosclerosis. Journal of the American College of Cardiology. 2004;**44**(9):1819-1824

[54] Martinez-Martinez E et al. Leptin induces cardiac fibrosis through galectin-3, mTOR and oxidative stress: Potential role in obesity. Journal of Hypertension. 2014;**32**(5):1104-1114, discussion 1114

[55] Sweeney G. Leptin signalling. Cellular Signalling. 2002;**14**(8):655-663

[56] do Carmo JM et al. Neuronal suppressor of cytokine signaling 3: Role in modulating chronic metabolic and cardiovascular effects of leptin. Hypertension. 2018;**71**(6):1248-1257

[57] Abel ED, Sweeney G. Modulation of the cardiovascular system by leptin. Biochimie. 2012;**94**(10):2097-2103

[58] Sweeney G. Cardiovascular effects of leptin. Nature Reviews. Cardiology. 2010;**7**(1):22-29

[59] Chatham JC, Seymour AM. Cardiac carbohydrate metabolism in Zucker diabetic fatty rats. Cardiovascular Research. 2002;**55**(1):104-112

[60] Wende AR, Abel ED. Lipotoxicity in the heart. Biochimica et Biophysica Acta. 2010;**1801**(3):311-319

[61] Barbeau PA et al. Alpha-Linolenic acid and exercise training

independently, and additively, decrease blood pressure and prevent diastolic dysfunction in obese Zucker rats. The Journal of Physiology. 2017;**595**(13):4351-4364

[62] 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. 2006;**55**(8):1067-1075

[63] Stanley WC, Recchia FA. Lipotoxicity and the development of heart failure: Moving from mouse to man. Cell Metabolism. 2010;**12**(6):555-556

[64] Hall ME, Harmancey R, Stec DE. Lean heart: Role of leptin in cardiac hypertrophy and metabolism. World Journal of Cardiology. 2015;**7**(9):511-524

[65] Abe Y et al. Leptin induces elongation of cardiac myocytes and causes eccentric left ventricular dilatation with compensation. American Journal of Physiology. Heart and Circulatory Physiology. 2007;**292**(5):H2387-H2396

[66] Barouch LA, Berkowitz DE, Harrison RW, O'Donnell CP, Hare JM. Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. Circulation. 2003;**108**(6):754-759

[67] Sawyer DB et al. Role of oxidative stress in myocardial hypertrophy and failure. Journal of Molecular and Cellular Cardiology. 2002;**34**(4):379-388

[68] Fortuno A et al. Is leptin involved in phagocytic NADPH oxidase overactivity in obesity? Potential clinical implications. Journal of Hypertension. 2010;**28**(9):1944-1950

[69] Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. The FASEB Journal. 1999;**13**(10):1231-1238

[70] Martinez-Martinez E et al. The potential role of leptin in the vascular remodeling associated with obesity. International Journal of Obesity. 2014;**38**(12):1565-1572

[71] Zibadi S, Cordova F, Slack EH, Watson RR, Larson DF. Leptin's regulation of obesity-induced cardiac extracellular matrix remodeling. Cardiovascular Toxicology. 2011;**11**(4):325-333

[72] Khaidar A, Marx M, Lubec B, Lubec G. L-arginine reduces heart collagen accumulation in the diabetic db/db mouse. Circulation. 1994;**90**(1):479-483

[73] Fredersdorf S et al. Myocardial hypertrophy and enhanced left ventricular contractility in Zucker diabetic fatty rats. Cardiovascular Pathology. 2004;**13**(1):11-19

[74] Aroor AR et al. Dipeptidyl peptidase-4 (DPP-4) inhibition with linagliptin reduces western diet-induced myocardial TRAF3IP2 expression, inflammation and fibrosis in female mice. Cardiovascular Diabetology. 2017;**16**(1):61

[75] Wang X et al. Pharmacogenomic, physiological, and biochemical investigations on safety and efficacy biomarkers associated with the peroxisome proliferator-activated receptor-gamma activator rosiglitazone in rodents: A translational medicine investigation. The Journal of Pharmacology and Experimental Therapeutics. 2010;**334**(3):820-829

[76] Takahashi K et al. Roles of oxidative stress and the mineralocorticoid receptor in cardiac pathology in a rat model of metabolic syndrome. Nagoya Journal of Medical Science. 2015;**77**(1-2):275-289

[77] Martinez-Martinez E et al. The lysyl oxidase inhibitor (beta-aminopropionitrile) reduces leptin profibrotic effects and ameliorates cardiovascular remodeling in diet-induced obesity in rats. Journal of Molecular and Cellular Cardiology. 2016;**92**:96-104

[78] Rodriguez C et al. Regulation of lysyl oxidase in vascular cells: Lysyl oxidase as a new player in cardiovascular diseases. Cardiovascular Research. 2008;**79**(1):7-13

[79] Li H et al. Inflammatory biomarkers of coronary heart disease. Frontiers in Bioscience (Scholar Edition). 2018;**10**:185-196

[80] Martin SS, Qasim A, Reilly MP. Leptin resistance: A possible interface of inflammation and metabolism in obesity-related cardiovascular disease. Journal of the American College of Cardiology. 2008;**52**(15):1201-1210

[81] Yamagishi SI et al. Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acid oxidation via protein kinase a. The Journal of Biological Chemistry. 2001;**276**(27):25096-25100

[82] O'Rourke L, Gronning LM, Yeaman SJ, Shepherd PR. Glucose-dependent regulation of cholesterol ester metabolism in macrophages by insulin and leptin. The Journal of Biological Chemistry. 2002;**277**(45):42557-42562

[83] Lam QL, Lu L. Role of leptin in immunity. Cellular & Molecular Immunology. 2007;**4**(1):1-13

[84] Faulkner JL, Bruder-Nascimento T, Belin de Chantemele EJ. The regulation of aldosterone secretion by leptin: Implications in obesity-related cardiovascular disease. Current Opinion in Nephrology and Hypertension. 2018;**27**(2):63-69

[85] Vatutin NT, Shevelok AN. Relationship between blood aldosterone

and somatometric parameters in patients with chronic heart failure and preserved ejection fraction of left ventricle. Klinicheskaia Meditsina. 2016;**94**(4):265-269

[86] Olivier A et al. Effect of eplerenone in patients with heart failure and reduced ejection fraction: Potential effect modification by abdominal obesity. Insight from the EMPHASIS-HF trial. European Journal of Heart Failure. 2017;**19**(9):1186-1197

[87] Beltowski J. Leptin and the regulation of renal sodium handling and renal Na-transporting ATPases: Role in the pathogenesis of arterial hypertension. Current Cardiology Reviews. 2010;**6**(1):31-40

[88] Hall JE, do Carmo JM, da Silva AA, Wang Z, Hall ME. Obesity-induced hypertension: Interaction of neurohumoral and renal mechanisms. Circulation Research. 2015;**116**(6):991-1006

[89] Hall JE, Hildebrandt DA, Kuo J. Obesity hypertension: Role of leptin and sympathetic nervous system. American Journal of Hypertension. 2001;**14** (6 Pt 2):103S-115S

[90] Huby AC et al. Adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. Circulation. 2015;**132**(22):2134-2145

[91] Xue B et al. Leptin mediates high-fat diet sensitization of angiotensin II-elicited hypertension by upregulating the brain renin-angiotensin system and inflammation. Hypertension. 2016;**67**(5):970-976

[92] Natarajan R, Ploszaj S, Horton R, Nadler J. Tumor necrosis factor and interleukin-1 are potent inhibitors of angiotensin-II-induced aldosterone synthesis. Endocrinology. 1989;**125**(6):3084-3089

[93] Belin de Chantemele EJ, Mintz JD, Rainey WE, Stepp DW. Impact of leptin-mediated sympatho-activation on cardiovascular function in obese mice. Hypertension. 2011;**58**(2):271-279

[94] Huby AC, Otvos L Jr, Belin de Chantemele EJ. Leptin induces hypertension and endothelial dysfunction via aldosterone-dependent mechanisms in obese female mice. Hypertension. 2016;**67**(5):1020-1028

[95] Hofmann A et al. Elevated steroid hormone production in the db/db mouse model of obesity and type 2 diabetes. Hormone and Metabolic Research. 2017;**49**(1):43-49