HHS Public Access

Author manuscript

Curr Opin Nephrol Hypertens. Author manuscript; available in PMC 2018 July 20.

Published in final edited form as:

Curr Opin Nephrol Hypertens. 2018 March ; 27(2): 63–69. doi:10.1097/MNH.0000000000000384.

The regulation of aldosterone secretion by leptin: implications in obesity-related cardiovascular disease

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Abstract

Purpose of review—Although it has been known for some time that increases in body mass enhance aldosterone secretion, particularly in women, the origin of this elevation in aldosterone production is not well defined. Adipocyte-derived factors have emerged as potential candidates to increase aldosterone production in obesity.

Recent findings—Emerging evidence suggests the presence of a mechanistic link in which the adipocyte-derived hormone leptin stimulates aldosterone production in obesity, thereby creating a positive feedback loop for obesity-associated cardiovascular disease. In addition, recent reports give credence to the concept that this leptin–aldosterone stimulation pathway in obesity is an underlying mechanism for sex-discrepancies in obesity-associated cardiovascular disease.

Summary—Leptin appears as a new direct regulator of adrenal aldosterone production and leptin-mediated aldosterone production is a novel candidate mechanism underlying obesity-associated hypertension, particularly in females.

Keywords

aldosterone; hypertension; leptin; obesity; sex differences

INTRODUCTION

Aldosterone levels are characteristically upregulated in obese patients. Although obesity is characterized by a dysfunction of many hormone systems, obesity-associated increases in circulating aldosterone is not particularly associated with disruption of aldosterone's classical activators: angiotensin II (ANGII), plasma potassium level and adrenocorticotropin release. Many studies have suggested the existence of an adipocyte-derived aldosterone-stimulating factor, and subsequently, the adipocyte-derived hormone leptin has emerged as a major candidate mechanism underlying increases in aldosterone secretion in the obesity condition. This review will discuss evidence in the literature for the presence of a link

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Conflicts of interest

There are no conflicts of interest.

between leptin and aldosterone secretion, as well as the contribution of leptin-mediated aldosterone secretion in cardiovascular disease.

THE IDENTIFICATION OF AN ADIPOCYTE-DERIVED ALDOSTERONE-SECRETING FACTOR IN OBESITY: EVIDENCE IMPLICATING LEPTIN IN THIS ROLE

It was observed several decades ago that obesity is associated with an increase in aldosterone, which has since been confirmed by a large number of clinical and basic science studies [1–4]. This is also true in rodents as high-fat diet-induced obese mice present with a higher level of aldosterone compared with lean mice [5,6]. The positive relationship of aldosterone to body mass is evidently specific to the adipose tissue. Studies have shown that adiposity itself is directly correlated to plasma aldosterone levels in an American population [3] as well as additionally tied to adiposity-associated hypertension in African-American and French Canadian patients [7]. Although these studies have evaluated both men and women, others have uncovered sex-dependent relationships of body mass and aldosterone. In an elegant study, Goodfriend *et al.* [3] analyzed the correlation between aldosterone plasma levels and fat mass in normotensive women and normotensive men and found that plasma aldosterone in women correlates directly with visceral adipose tissue, independent of plasma renin activity, whereas no correlation is evident in men. Following a weight-loss regimen, significant reductions in plasma aldosterone are observed in both sexes; however, the correlation of aldosterone with adipose tissue persists in women, potentially indicating a cause-and-effect relationship that may be sex-specific. [3].

Aldosterone is primarily synthesized in and secreted from the outer layer of the adrenal cortex, the zona glomerulosa, although, secondary sources of aldosterone have been identified including adipose tissue itself [2,4]. Aldosterone secretion is traditionally regulated by three factors: plasma potassium, ANGII and adrenocorticotropin, as has been reviewed elsewhere [8]; however, several studies have indicated that these factors are not directly correlated with aldosterone in obese patients [9–14]. Many studies have confirmed that aldosterone production is correlated with adipose tissue mass, particularly white adipose tissue [15]. It was later confirmed that an adipocyte-derived aldosterone-stimulating factor is present in rodents [16], and in addition, that the presentation of obesity in rodents increases the production of this factor [16]. The establishment of this concept led to the suggestion of an adipose-derived aldosterone secretion factor. Ehrhart-Bornstein *et al.* [17] then investigated the direct effects of adipocytes on adrenocortical aldosterone release and cocultured NCI-H295R adrenocortical cells with media from adipocyte cultures and observed that aldosterone production was increased. These studies indicate that factor(s) upregulated by and derived from adipose tissue stimulates increased aldosterone production, which prompted investigation into the role of adipocyte-derived hormones (‘adipokines’) and their role in aldosterone regulation.

Leptin is an adipokine whose levels increase in accordance with increasing adipose mass and is dramatically increased in obesity, which made leptin a candidate for an aldosterone-stimulating factor. Our first finding indicating that leptin may be implicated in aldosterone

secretion was observed in male C57Bl/6 mice, in which we found that leptin infusion (10 μg/day) increases aldosterone plasma levels in mice on a control and high-fat diet, data that have been recapitulated in female mice [5,18▪▪]. These data were strengthened by a similar finding in protein tyrosine phosphatase 1b (PTP1b) knockout mice, a model of leptin hypersensitivity, PTP1b being an endogenous molecular restraint of the leptin-signaling pathway. In PTP1b knockout female mice we observed that leptin hypersensitivity *per se* triggers aldosterone production, as well as adrenal *CYP11B2* (aldosterone synthase) expression [18▪▪]. The studies that followed this observation were published in the same report in which we found that aldosterone levels were increased in correlation with increasing leptin levels in both Agouti female hyperleptinemic mice, which are hyper-phagic and obese because of a mutation in the leptin-mediated appetite suppression pathway, as well as high-fat diet-induced obese female mice, which are hyperleptinemic [18▪▪]. To further confirm the role of leptin as a mediator of this obesity-associated elevation in aldosterone in obese female mice, we measured aldosterone in three rodent models of obesity in which leptin activity is deleted: *ob/ob* mice (deficient in leptin), *db/db* mice (deficient in leptin receptor) and Zucker rats (expressing a nonfunctional leptin receptor), all of which failed to have increased aldosterone plasma level and adrenal *CYP11B2* gene or protein expression despite the presence of obesity [18▪▪]. Furthermore, administration of the leptin receptor antagonist Allo-Aca blunts elevated aldosterone plasma levels in female PTP1b knockout mice and obese Agouti mice [19▪▪] suggesting that leptin receptor activation mediates aldosterone production. These data demonstrate that increases in aldosterone production observed in obese mice are independent of obesity *per se*, but rather dependent on leptin signaling. Other reports show conflicting data with regard to these models and their respective aldosterone levels [2,4,20–22]. The reason for the discrepancy between our findings and others remains unclear. The strength of our data resides in the diversity of the animals (mouse and rats) and of the genetic backgrounds (Balb/c, C57Bl/6, Agouti) all housed in the same animal facility and fed an identical diet (0.2% Sodium, Teklad Global #2018).

Although leptin receptors are expressed in a variety of cell types and organ systems, recent data indicates that the leptin-aldosterone stimulation pathway is a direct relationship, and unlikely involving a secondary mediator. We [18▪▪] and others [23–25] have shown that leptin receptors are expressed in adrenal tissues of humans and rodents. Our study specifically showed that leptin receptors are colocalized with *CYP11B2* in human adrenal cortical cells, implying that the regulation of aldosterone secretion in the adrenal cortex by leptin signaling is a more direct relationship mediated by the leptin–*CYP11B2* interaction in adrenal cells [18▪▪] (Fig. 1). This direct relationship of leptin-mediated aldosterone secretion is suggested by evidence of a concentration-dependent increase in aldosterone production and *CYP11B2* expression in human adrenal zona glomerulosa cells *in vitro* [18▪▪]. Leptin-mediated release of aldosterone by adrenal cells also appears to be a calcium-dependent process, in a similar fashion to ANG Il-induced aldosterone production. Similar to ANG II, leptin increases calmodulin and calmodulin-dependent protein kinase expressions in HAC15 cells (human adrenocortical carcinoma cell line) [18▪▪]. Furthermore, chelating the intracellular Ca^{2+} with BAPTA-AM abolishes leptin-mediated as well as ANG II-mediated increases in *CYP11B2* promoter activity suggesting that leptin-mediated aldosterone

production is Ca^{2+} maneuver-dependent [18▪▪]. However, further data are required to determine the exact intracellular pathways that mediate the leptin–*CYP11B2* aldosterone-stimulating relationship. The single direction (i.e. not a feedback mechanism) implied by these findings are strengthened by data in human patients with alterations in aldosterone signaling. Neither patients with congenital adrenal cortical hyperplasia (aldosterone deficiency) [26] nor those with primary aldosteronism (elevated aldosterone levels) [27,28] present with correlating alterations in leptin levels, indicating that the stimulation of aldosterone by leptin is not a circular feedback mechanism in a physiological system.

Although it is tempting to simplify that hyperleptinemia alone leads to hyperaldosteronism in obesity, it is unlikely that leptin is the only adipokine contributing to aldosterone secretion in obese patients. Other adipocyte-derived products, such as the innate immune cytokine interleukin-6, may play a role in aldosterone secretion [29,30], and is also notably increased in obesity, particularly visceral adiposity [31]. In addition, Bollag and colleagues have demonstrated that very low-density lipids (VLDL) are capable of stimulating *CYP11B2* expression and aldosterone secretion in different adrenal cell model systems such as: primary cultures of human and bovine adrenal cells and the adrenocortical cell line H295R [32]. Therefore, further investigation is needed into the individual contributions of various obesity-associated factors, including leptin, that stimulate hyperaldosteronism in obesity.

FEMALE PREDOMINANCE OF THE LEPTIN–ALDOSTERONE AXIS

Women characteristically have an increased leptin level per unit of body mass [33,34] compared with men. In accordance, aldosterone rises in obese women are more correlated to body mass in women compared with men [3]. Additionally, in rodents, only female PTP1B knockout leptin-sensitive mice have elevated aldosterone levels and adrenal *CYP11B2* expression [18▪▪], indicating a heightened leptin–aldosterone stimulation in female mice that begins with an increased production of leptin. As the leptin–aldosterone stimulation pathway has only recently been proposed, the evolutionary basis for the sex discrepancy in this relationship is speculative at this point, but may be tied to fertility needs that are unique to women.

As has been reviewed elsewhere [35], leptin likely serves as a ‘nutrition sensing’ hormone in women, indicating adequate adipose stores for fertility. Animal models as well as human studies have demonstrated that adequate leptin signaling is required for reproductive puberty to progress in females [36,37]. In addition, leptin follows a cyclical pattern throughout the menstrual cycle in women, peaking at the luteal phase [38], in correlation with the cyclical pattern of aldosterone [39], which is the phase during which embryonic implantation occurs. Pregnancy is a state of heightened physiological need for salt and fluid retention to sustain blood volume expansion [40]. A steady rise in leptin levels is observed throughout all three trimesters, in correlation with trends of rising aldosterone levels throughout pregnancy, indicating that leptin may contribute to rising aldosterone levels [40,41]. The potential function of this role for leptin-induced aldosterone in pregnancy is demonstrated in mice lacking *CYP11B2*, which are unable to maintain adequate blood pressure to sustain fetal growth [42]. Although ANG II levels are also increased in pregnancy, plasma renin activity peaks in early trimesters of a healthy pregnancy whereas aldosterone levels peak in the third

trimester [40]. Furthermore, angiotensin II type I receptor (AT1R) sensitivity is reduced in a normal pregnancy [43], and it may be postulated that leptin predominates as the primary aldosterone-stimulating factor in late pregnancy, however, if adrenal AT1R sensitivity is also reduced in normal pregnancies is in need of investigation.

CARDIOVASCULAR CONSEQUENCES OF THE ACTIVATION OF THE LEPTIN–ALDOSTERONE AXIS: IMPLICATIONS PREDOMINANTLY FOUND IN FEMALE ANIMALS

Increasing BMI is associated with a heightened risk for cardiovascular disease in both sexes, however, the mechanisms underlying the development of obesity-associated cardiovascular diseases are likely sex-specific. It is well established that leptin induces increases in sympathetic tone and hypertension in obese men, however, a comparable increase in sympathetic activation in obese female animals who are not postmenopausal has not been similarly observed [44–46]. What is common among both sexes is the contribution of leptin to obesity-associated hypertension, as animal models as well as human studies have indicated that hyperleptinemia contributes to increased blood pressure [5,47–49]. Therefore, an alternative mechanism to leptin-induced sympathetic activation is likely implicated in obesity-associated hypertension in female animals and emerging evidence suggests the leptin–aldosterone stimulation pathway may be this key mechanism.

Clinical studies have shown that obese women are more responsive to the blood pressure-lowering effects of mineralocorticoid receptor antagonists than obese men [50], indicating that this pathway plays a significant role in vascular tone in women in obesity. At this time, no clinical report has investigated sex differences in leptin inhibition on blood pressure in the clinical population, however, emerging data indicates a need for such studies.

Our recent works have shown that leptin mediates aldosterone production in association with induction of endothelial dysfunction, cardiac fibrosis and hypertension in female mouse models. Female Balb/C wild-type mice infused with leptin (0.9 mg/kg/day) present with endothelial dysfunction and increased cardiac pro-fibrotic markers after 7 days of treatment [18▪▪]. Importantly, mineralocorticoid receptor blockade with spironolactone blunts leptin-mediated endothelial dysfunction and increased cardiac fibrosis in female mice [18▪▪]. Affirming that elevations in leptin are critical for obesity-induced vascular dysfunction in obese female mice, female *ob/ob* mice do not spontaneously present with vascular and cardiac abnormalities, however, leptin replacement in *ob/ob* female mice induces endothelial dysfunction and elevates pro-fibrotic cardiac markers, which is prevented by concurrent spironolactone treatment [18▪▪]. We also have shown that leptin sensitization with PTP1b deletion or high leptin levels in Agouti female mice promotes impaired vascular dilation to acetylcholine (a measure of endothelial dysfunction) and elevates mean arterial pressure. In addition, pharmacological leptin receptor antagonism (Allo-Aca) reverts impaired endothelial dilation and reduces high blood pressure in both PTP1b knockout and Agouti mouse models [19▪▪]. No development of endothelial dysfunction presents spontaneously in male PTP1b knockout or Agouti mice, indicating that female leptin-sensitive and hyperleptinemic mice are more responsive to the vascular effects of the leptin–aldosterone

stimulation pathway. Taken together, these data indicate that leptin induces cardiovascular dysfunction by increasing aldosterone production in the adrenal glands exclusively in female mice (Fig. 2). Although many have attributed increased leptin production in women to their predisposition of subcutaneous adipose tissue, further studies are needed to establish mechanistic pathways via which the leptin–aldosterone stimulation pathway is not only more efficient in women to produce aldosterone, but also mechanisms describing the increased sensitivity female mice have for the pro-hypertensive effects of aldosterone.

CONCLUSION

Dysregulation of the renin–angiotensin–aldosterone system has been well characterized in obesity and it has long been known that aldosterone levels are increased, however, these emerging data tie together for the first time an apparent role for leptin as a novel regulator of aldosterone production. The implications of this relationship appear to be more heavily pronounced in women as they have increased production of both hormones in obesity and evidence in animal models indicates that the cardiovascular effects of this relationship are especially impactful in obese female mice. The implications of this relationship have a significant potential impact as pharmaceutical agents suppressing aldosterone activation (i.e. mineralocorticoid receptor antagonists) are currently commercially available and may be on the advent of becoming an aspect of personalized medicine treatment for obese women at risk for cardiovascular disease.

Acknowledgements

We would like to thank Lynsey Ekema, MSMI, CMI, Department of Technology Enhanced Learning and Innovation at Augusta University, for assistance in preparing the medical illustration.

Financial support and sponsorship

This work was supported by NIH 1R01HL130301–01, AHA 16IRG27770047, 1 F32 HL136191–01A1 and AHA 17POST33410363.

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KEY POINTS

- Emerging evidence suggests that obesity-induced increases in aldosterone production are mediated by increases in leptin production in obesity.
- Leptin-induced aldosterone secretion is a novel pathway that may have significant effects on the development of cardiovascular disease in obesity.
- Leptin-induced aldosterone production contributes to obesity-associated hypertension and endothelial dysfunction in a sex-specific manner, predominately in female.

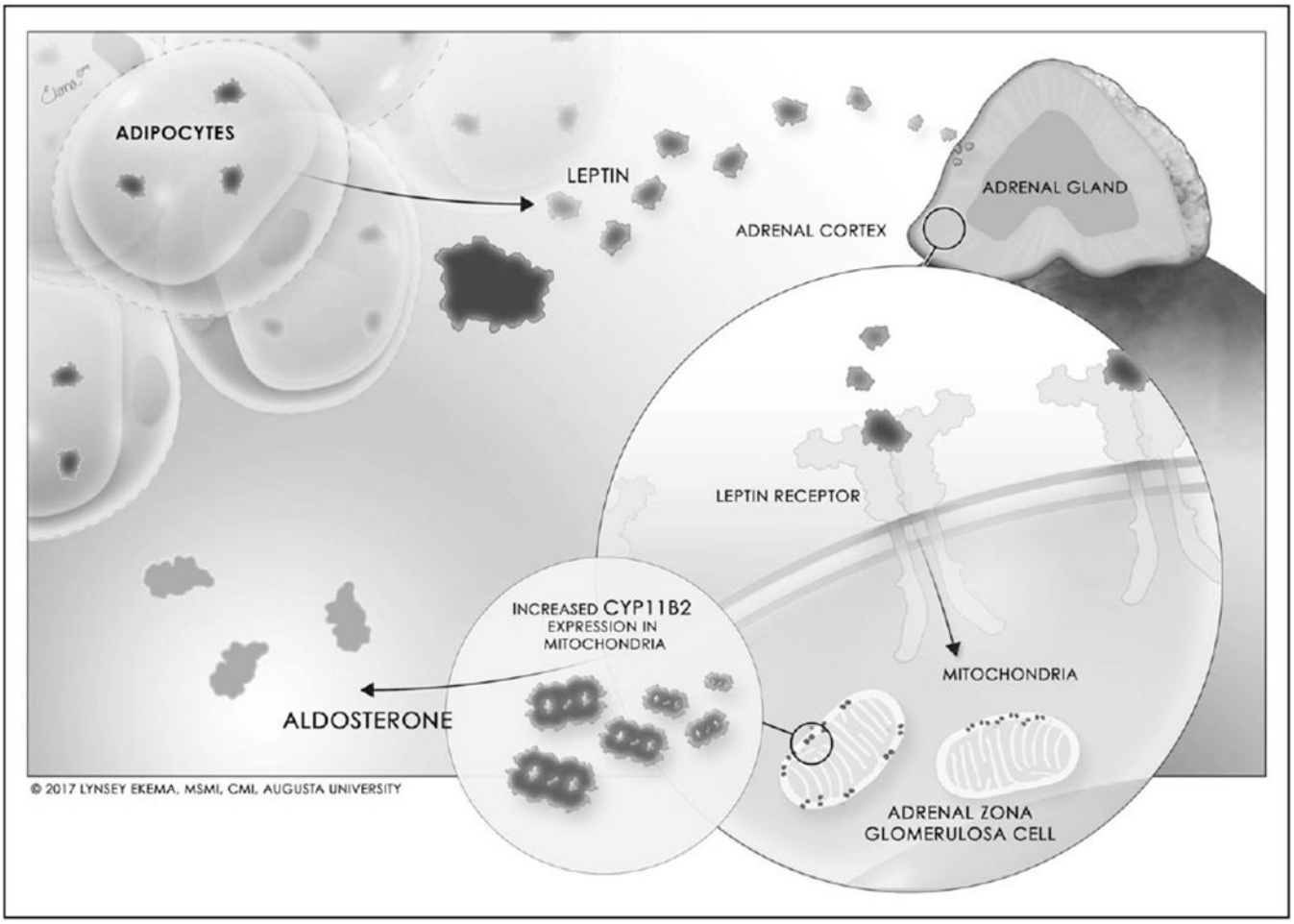

FIGURE 1.
Regulation of aldosterone secretion by leptin.

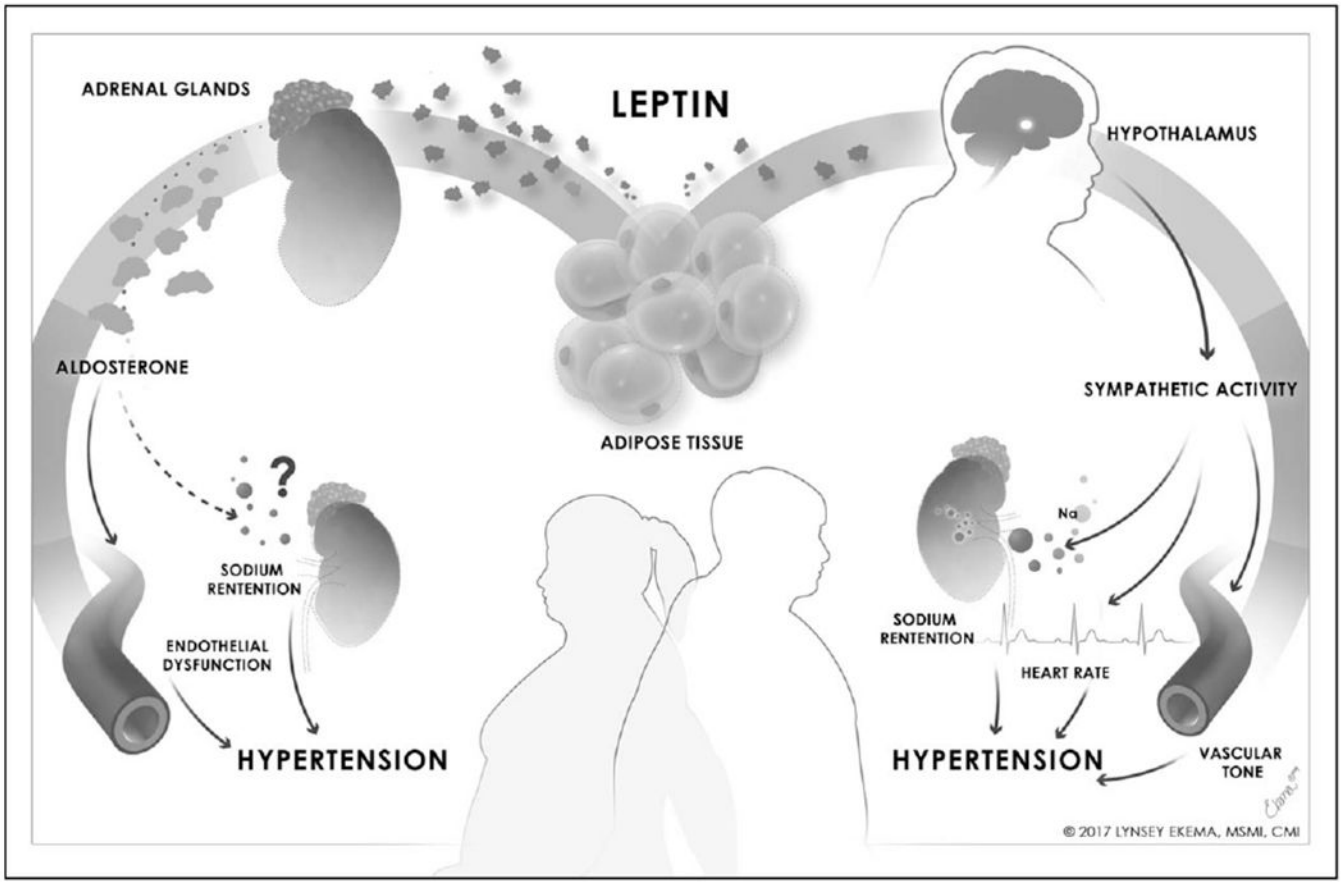

FIGURE 2.
Proposal for sex differences in obesity-associated leptin-mediated hypertension.