Brief Review

Sex Differences in Mechanisms of Hypertension Associated With Obesity

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Obesity is on a fast track to become the most costly and burdensome health epidemic worldwide. Comorbidities associated with obesity include type II diabetes mellitus and cardiovascular disease (CVD), of which hypertension is a highly prevalent and significant risk factor. Rising hypertension rates in both men and women are closely correlated with, and largely attributable to, rising rates of obesity.[1,2] Currently, ≤70% of essential hypertension cases are associated with obesity.[1] Understanding the mechanisms that lead to obesity-associated hypertension is vital to treat this growing patient population. However, there is a significant deficit of reports examining sex differences in obesity-associated hypertension in the literature to date because research efforts have been overwhelmingly restricted to male animals, and many clinical reports fail to separate results by sex. The National Institutes of Health, American Heart Association, and others have begun to raise awareness of sex discrepancies in research, and as a result, there has been an increase in publications highlighting differences in mechanisms associated with obesity-associated hypertension in females versus males. This review will summarize current knowledge of (1) epidemiological data of sex discrepancies in obesity-associated hypertension, (2) the sex specificity of the effects of obesity on sympathoactivation and its role in hypertension, (3) the potential role of leptin in sex differences in obesity-associated hypertension, (4) the influence of female sex hormones on leptin and obesity-associated hypertension, and (5) sex differences in renin–angiotensin–aldosterone system activation in obesity.

Risk of Obesity-Associated Hypertension Is Sex-Specific

Population rates of obesity are not equal between men and women. Data from the NHANES study (National Health and Nutrition Examination Survey),[3–5] REGARDS study (Reasons for Geographic and Racial Differences in Stroke),[6] and Jackson Heart Study[7] demonstrate that women have a higher obesity rate than men. Worldwide, the prevalence of obesity in women is higher than men in countries of all socioeconomic status, especially in Middle-Eastern and Northern African countries.[8] In addition, there is a disparity in the severity of obesity between men and women, with the risk of class III obesity (body mass index [BMI] >40 kg/m²) being 50% higher in women.[6,9,10] Although these sex differences are well documented, the population health implications brought on by higher rates of obesity in women are not well represented by obesity research, which has disparately preferred male subjects.

Obesity is a significant risk factor for CVD, the leading cause of death in both sexes. Hypertension is a significant predictor of CVD events and mortality.[11,12] Emerging data indicate that the impact of obesity on blood pressure (BP), that is, cardiovascular health, is disproportionate in women compared with that in men.[13] Studies in Japanese,[14] Native American[15] populations, and others[16] demonstrate that hypertension is more strongly associated with obesity in women than men, particularly morbid obesity. Importantly, there are likely variations in the effects of obesity on hypertension risk in women based on ethnicity; however, further study is needed to uncover these ethnic variances. The lifetime risk of hypertension is also higher in women than in men, with obesity cited as the most significant risk factor.[17] BP is also less likely to be adequately controlled in obese women than men.[18,19] Therefore, the overall healthcare burden of obesity-associated hypertension in women likely exceeds that of men.

Many have shown that the primary ages of CVD risk in women are those in post-menopause. Indeed, the risk of hypertension is lower in women than men at young ages (≈<50 years) but with a reversal in postmenopausal ages,[9,20] which gives credence to the current dogma that women are protected from hypertension until menopausal ages. However, this perceived protection may be restricted to lean premenopausal women because it has been observed that BP is more heavily associated with increasing BMI in young obese women.[13,21–24] Therefore, whether premenopausal or not, the risk of hypertension associated with obesity in women is a significant public health concern.

Sympathetic Activity Is Upregulated in Obesity in Males and Postmenopausal Women

There is a consensus that sympathetic activation is ubiquitously activated in obese men. Many studies have confirmed that increases in BMI are directly correlated with an increased sympathetic-mediated heart rate[25] and muscle sympathetic nerve activity, which is reversible with weight loss.[25–29] In contrast, sympathetic activation is not characteristically activated in obese premenopausal women. Neither BMI[26,29,30] nor waist circumference (a measure of visceral adiposity)[26] is directly correlated with muscle sympathetic nerve activity in women, and weight loss reduces muscle sympathetic nerve activity only in men.[29] Interestingly, these sex discrepancies

may vary based on racial and ethnic background, as shown by Abate et al[31] in their study in which black men did not display BMI-associated increases in sympathetic activity comparable to white men. The sex differences in obesity-associated sympathetic activation have been reviewed in excellent detail elsewhere.[30,32–34]

Sympathetic tone in obesity is at least partially regulated by adipose deposition locale. Women of all ages have increased adipose tissue mass compared with men, albeit distribution patterns change with menopause.[35–37] In addition, women, particularly before menopause, preferentially deposit adipose in subcutaneous depots rather than viscerally.[38] A given mass of visceral adipose is associated with a greater increase in muscle sympathetic nerve activity than the same mass of adipose of a different depot,[39–41] which is particularly evident in that increasing visceral adipose in postmenopausal women[42–46] is associated with increased sympathetic nervous system tone.[47] Sex differences in sympathetic nervous system activation in association with obesity are, therefore, dependent not only on sex but also on menopausal status. The remainder of this review will discuss other sex-specific obesity-associated mechanisms implicated in hypertension in women.

Leptin Contributes to Obesity-Associated Hypertension via Sex-Specific Mechanisms

Leptin was the first identified adipokine (adipose-derived cytokine) and has a significant role in BP regulation in obesity. In both males and females, mutations in the human leptin gene[48,49] or global deficiency in leptin (*Ob/Ob*) or leptin receptors (*Db/Db*) in rodents[50,51] results in obesity, hyperphagia, and hyperinsulinemia, but notably not hypertension, suggesting that obesity per se does not increase BP but rather that leptin is required for obesity-associated increases in BP. Females have higher leptin levels and leptin receptor (ObR) expression compared with males after adjusting for age, BMI, and body fat percentage, indicating that female adipocytes release more leptin per gram of adipose mass.[52–54] Subcutaneous adipose tissue is a more potent leptin-producing organ than visceral adipose,[54] and leptin levels are inversely correlated with a higher waist–hip ratio, which is lower in women compared with men.[55] As subcutaneous adipose predominates in

women, this may account for a sharper rise in leptin levels with increasing BMI compared with men.[54,56]

Published data give credence that sympathetic activation mediated by hypothalamic neural stimulation mediates leptin-induced hypertension in males (Figure).[27,57] This concept is supported by data showing that male mice with impaired leptin signaling do not develop hypertension or elevated sympathetic activity despite severe obesity.[58] In male experimental animals, leptin induces sympathetic activation through activation of hypothalamic leptin receptors, ultimately leading to increased BP, which has been thoroughly reviewed.[59]

The neuronal pathways that mediate rises in BP in response to leptin are somewhat controversial. Leptin receptors are expressed in various hypothalamic regions of the brain, notably the proopiomelanocortin neurons of the arcuate nucleus. Proopiomelanocortin leptin receptor activation stimulates the MC4R (melanocortin 4 receptor) via release of its endogenous ligand, α-melanocyte–stimulating hormone.[60] These actions of leptin mediate its anorexic effects and have been proposed to mediate its effects on BP in male animals as well.[61] Hall et al[59] demonstrated that male MC4R-deficient mice do not develop hypertension despite severe obesity and hyperleptinemia, suggesting that this signaling pathway is crucial for leptin-mediated hypertension. However, whether sympathetic activation, and therefore BP increases, in male mice is mediated exclusively by leptin-derived MC4R activation is not as clear cut as implied in these studies. Male Agouti mice, a model of leptin resistance whom develop obesity via the production of a natural antagonist to the MC4R and MC3R, develop an increase in BP compared with lean mice.[62,63] The contrast between these data is likely derived from 1 of 2 explanations. The first is that the MC4R-deficient model eliminates all MC4R activity, whereas the Agouti peptide is specifically an inverse agonist, preserving some (albeit not maximal) activation of the MC4R. The second, as described by Bełtowski et al,[64] is that natriuretic effects of the MC3R in the hypothalamus are preserved in the MC4R-deficient model, whereas the Agouti peptide inhibits the actions of this receptor. The role of the MC4R in sympathetic activation in males is also evident by the presentation of high BP in the Zucker obese rat. Zucker rats exhibit a mutated leptin receptor
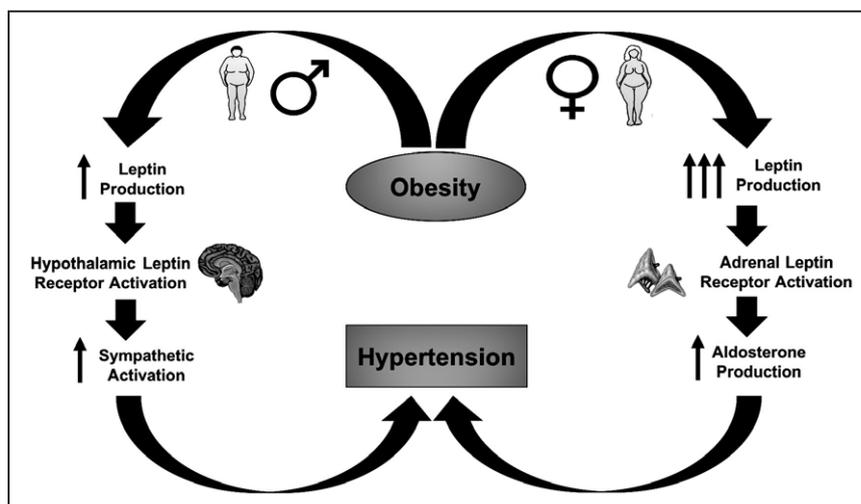
Figure. Schematic of candidate mechanisms of leptin-induced hypertension in men and women.

and spontaneously develop obesity, and paradoxically, have been shown to develop both an increase in BP and sympathetic activation, in contrast to mouse models of leptin receptor deficiency.[65] However, do Carmo et al[66] demonstrated that BP increases in these rats depends on activation of MC4R signaling, indicating that the Zucker rat possesses a specific mechanism endogenously increasing sympathetic activation independent of leptin. The identification of this mechanism may shed light on mechanisms of leptin resistance in males. Collectively, these studies demonstrate the need for further investigation into leptin-induced hypertension in the context of obesity, even in males.

The pathway via which leptin leads to hypertension in females is even more poorly understood. The PTP1b (protein tyrosine phosphatase 1b)-deficient mouse develops enhanced sensitivity to the leptin receptor via knockout of negative feedback mechanisms at the leptin receptor.[67] Leptin receptor antagonism blunts hypertension in both lean female PTP1b knockout mice and obese female Agouti hyperleptinemic mice,[63] indicating that leptin signaling mediates increases in BP in obese females. However, despite increased leptin production in women compared with that in men, neither leptin levels nor obesity are associated with an increase in sympathetic activation in women.[68,69] In experimental models, circulating norepinephrine levels are actually decreased in female PTP1b-deficient mice and unchanged in female Agouti obese mice compared with lean female mice.[63] Our laboratory has shown that obesity exacerbates BP reduction in response to ganglionic blockade in male Agouti mice, whereas BP response to ganglionic blockade is blunted in female Agouti mice, indicating that obesity and hyperleptinemia do not increase BP via neurogenic mechanisms in females.[63] In addition, obese female MC4R-deficient rats develop hypertension,[70] in contrast to male MC4R-deficient mice,[71] indicating that the leptin-MC4R hypothalamic pathway does not mediate hypertension in obese females. Therefore, leptin is required for obesity-associated hypertension in both males and females, but sympathetic nervous system and MC4R activation is not implicated in leptin-induced hypertension in obese females, which indicates that other leptin-derived mechanisms are implicated in obese hypertensive women.

Aldosterone May Be a Sex-Discrepant Mechanism Implicated in Obesity-Associated Leptin-Induced Hypertension

A novel pathway via which leptin may mediate hypertension in obese women is via activation of the aldosterone–mineralocorticoid receptor (MR) axis (Figure). Peripheral effects of MR activation outside of its role in renal sodium retention have been identified and linked with hypertension and vascular dysfunction in obesity in males and females.[72,73] Aldosterone levels increase in correlation with adipose tissue and BMI more so in females than in males.[74] Aldosterone and leptin levels correlate in obese hypertensive patients,[75] and our laboratory has demonstrated that leptin receptors colocalize with aldosterone synthase (*CYP11B2*) in the adrenal cortex and that leptin receptor activation stimulates *CYP11B2* expression and aldosterone production.[76] Female leptin-sensitive (PTP1b KO) mice exhibit increased aldosterone levels and adrenal

CYP11B2 expression, which is absent in male counterparts, indicating that females are prone to leptin-induced aldosterone secretion in a sex-specific manner.[76,77]

It has been reported that MR antagonists are more efficacious as a cardiovascular therapy regimen in women compared with men.[78,79] In rodents, MR antagonism by spironolactone reduces BP in female PTP1b-deficient leptin-sensitive mice, while having no effect on BP in males.[63] Furthermore, female PTP1b-deficient mice and Agouti hyperleptinemic mice develop endothelial dysfunction, a significant risk factor for hypertension that is evidenced experimentally by an impaired vasodilation to acetylcholine. Spironolactone restores endothelial function in females of both models.[63] Neither Agouti nor PTP1b-deficient male mice develop endothelial dysfunction, in contrast, indicating a heightened vascular sensitivity to leptin-mediated endothelial dysfunction in females.[63] In addition, female *Ob/Ob* leptin-deficient mice do not develop endothelial dysfunction despite severe obesity; however, endothelial dysfunction is induced by leptin restoration in these mice and subsequently restored by MR antagonism.[76] Collectively, these data imply that leptin-induced hypertension in females may develop via an aldosterone-dependent mechanism that is at minimum associated with, if not caused by, endothelial dysfunction. Further studies, including those examining mechanisms of aldosterone sensitivity, are needed in males and females to distinguish the potential of the aldosterone–mineralocorticoid receptor pathway as a therapeutic preference for obese women.

Females Lose Protection From Female Sex Hormones in Obesity

Rates of CVD and hypertension are lower in premenopausal women as a whole compared with age-matched men.[9,20] Rising rates of hypertension in postmenopausal women have been attributed to losses of CVD protection by female sex hormones, as excellently reviewed elsewhere.[80] However, obese premenopausal women are not protected from hypertension compared with males. Wilsgaard et al[13] demonstrated that increases in BMI had a greater effect to increase BP in women compared with men, which was not associated with menopause. The odds ratio for hypertension strongly correlates with BMI in premenopausal women in a Taiwanese population as well.[21] In addition, the presence of type II diabetes mellitus, which is strongly associated with obesity, ablates the protective effects of female sex hormones from both hypertension and coronary heart disease.[23] Collectively, these data prompt studies of the mechanisms of desensitization of female sex hormone–mediated cardiovascular effects in obesity.

Estrogen, a well-established vasoprotective female sex hormone, is characteristically increased in obesity,[81,82] but cardiovascular protection is apparently lost. This contradictory pathophysiology in premenopausal obese women may be because of an offset balance favoring the prohypertensive effects of leptin, which begs the question of whether or not leptin and estrogen have interacting production pathways. Leptin is required for the development of puberty in young women and female mice,[83,84] and leptin levels increase in high estrogen states such as pregnancy[85] and the menstrual cycle.[86] Shi and Brooks[87] have suggested a functional relationship

between leptin and estrogen varying throughout the menstrual cycle. However, the data are not consistent. Rises in leptin do not necessarily follow the phases of the menstrual cycle in which estrogen levels are highest.[86] In addition, the literature is not consistent in demonstrating that leptin levels increase in women taking oral contraceptives.[88,89] These data indicate that the ability of estrogen to stimulate leptin, or vice versa, is likely a complex relationship, and further investigation is warranted.

Male sex hormones, notably testosterone, are positively associated with obesity in women.[90] The implications of these hormones in premenopausal obese women have primarily been investigated in the presence of polycystic ovarian syndrome, an obesity-associated androgen-overexpressing reproductive condition. Further experimental data are warranted into the direct effects of these male sex hormones in the presence of obesity-associated CVD.

Renin–Angiotensin System Contribution to Hypertension in Obesity Is Sex-Discrepant

The renin–angiotensin system (RAS) plays a significant role in obesity-associated hypertension in both men and women.[91,92] Activation of the RAS cascades from renal renin production and its catalysis of angiotensinogen to angiotensin I and ultimately angiotensin II, a vasoconstrictor and salt-retaining hormone. Angiotensin II also stimulates adrenal aldosterone production. In addition, alternative metabolism of angiotensin I via catalysis by ACE2 (angiotensin-converting enzyme 2) produces vasorelaxative angiotensin (1–7), whose activities are mediated through Mas receptors. Although the mechanisms are not clear, many have proposed that increased adipose tissue–derived RAS activation plays a role in the development of hypertension.[93,94] It is unknown whether sex differences in RAS activation in obesity is related to differences in salt handling because the efficacy of salt restriction in males and females depends on the age[95] and point in the menstrual cycle[96] of the sample population.

Sex differences in RAS-induced hypertension have been extensively reviewed elsewhere[97]; however, sex specificity of obesity-associated RAS activation is less well understood. An emerging concept pioneered by Gupte et al is that nonclassical pathways of the RAS, particularly vasoprotective angiotensin (1–7) activation, may play a role in obesity-associated hypertension in females. They showed that increasing adipose tissue in male and female mice results in sex-dependent angiotensin II, ACE2, and angiotensin (1–7) activations.[98] Plasma angiotensin II levels decreased, whereas angiotensin (1–7) levels were higher in female obese mice alone. Adipose ACE2 activity was elevated in female obese mice compared with males, indicating that adipose ACE2 contributes to angiotensin (1–7) production in female obese mice. Other reports by this team have suggested that deletion of the Mas receptor increases BP in obese female mice only, indicating that angiotensin (1–7) disruption may play a role in obesity-associated hypertension specifically in females.[99] In mouse models, estrogen has been shown to increase angiotensin (1–7) production in obese female mice,[99] indicating that this pathway may play a protective role when activated in premenopausal women, which begs the question of whether this system is dysregulated in hypertensive obese premenopausal women. Further studies are needed to investigate whether angiotensin (1–7) or Mas receptor expression are reduced in obese premenopausal women in association with increases in BP.

Conclusions

The determination of sex discrepancies in mechanisms of obesity-associated hypertension is of immense clinical importance as this population and its associated healthcare burden continues to grow worldwide. General first-line therapies for hypertension treatment include angiotensin II inhibition by angiotensin II type I receptor blockers or angiotensin-converting enzyme inhibitors,[100] and other commonly prescribed therapies include adrenergic blockade[101] and thiazide diuretics,[102] which are efficacious in many obese patients. However, the data presented in this article, as well as other clinical data,[72] indicate that other therapies, such as MR antagonists, may be more efficacious for obese women with hypertension.

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