Published in final edited form as:

Auton Neurosci. 2015 January ; 187: 18–26. doi:10.1016/j.autneu.2014.11.006.

Obesity-induced increases in sympathetic nerve activity: sex matters

Virginia L. Brooks¹, Zhigang Shi¹, Seth W. Holwerda², and Paul J. Fadel²

¹Department of Physiology and Pharmacology, Oregon Health & Science University, Portland, OR 97239

²Department of Medical Pharmacology and Physiology, Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO 65212

Abstract

Abundant evidence obtained largely from male human and animal subjects indicates that obesity increases sympathetic nerve activity (SNA), which contributes to hypertension development. However, recent studies that included women reported that the strong relationships between muscle SNA and waist circumference or body mass index (BMI) found in men are not present in overweight and obese women. A similar sex difference in the association between adiposity and hypertension development has been identified in animal models of obesity. In this brief review, we consider two possible mechanisms for this sex difference. First, visceral adiposity, leptin, insulin, and angiotensin II have been identified as potential culprits in obesity-induced sympathoexcitation in males. We explore if these factors wield the same impact in females. Second, we consider if sex differences in vascular reactivity to sympathetic activation contribute. Our survey of the literature suggests that premenopausal females may be able to resist obesity-induced sympathoexcitation and hypertension in part due to differences in adipose disposition as well as its muted inflammatory response and reduced production of pressor versus depressor components of the renin-angiotensin system. In addition, vascular responsiveness to increased SNA may be reduced. However, more importantly, we identify the urgent need for further study, not only of sex differences per se, but also of the mechanisms that may mediate these differences. This information is required not only to refine treatment options for obese premenopausal women but also to potentially reveal new therapeutic avenues in obese men and women.

Keywords

blood pressure; sex differences; leptin; insulin; visceral obesity; vasoconstriction

Correspondence: Virginia L. Brooks, Ph.D., Oregon Health & Science University, Department of Physiology and Pharmacology, L-334, 3181 SW Sam Jackson Park Rd, Portland, OR 97239, brooksv@ohsu.edu, Phone: 503-494-5843, Fax: 503-494-4352.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Obesity is a rapidly escalating epidemic that often leads to hypertension, due in part to increased sympathetic nerve activity (SNA) to muscle (MSNA) and the kidneys [for reviews, see (Davy & Orr, 2009; Esler et al., 2006; Lambert et al., 2010b)]. Moreover, elevated SNA may accelerate the progression of end organ damage (vascular, metabolic, cardiac, renal), independently of any rise in arterial pressure (AP) (Lambert et al., 2010a; Schlaich et al., 2009; Fisher et al., 2009). Thus, SNA may also contribute to the co-morbidities of insulin resistance, type II diabetes mellitus, obstructive sleep apnea, and cardiovascular disease commonly present in obese individuals. However, much of the current information documenting obesity-induced increases in SNA and AP have been obtained from male human and animal subjects. In this brief review, we highlight recent work beginning to explore potential sex differences and raise the question: does obesity increase SNA and AP in females, and if not, why not? As a basis for this discussion, we first provide a brief overview of what is known about sex differences in resting SNA and AP in non-obese healthy subjects.

Sex differences in SNA and AP

In young healthy lean subjects, women typically have lower levels of MSNA, directly measured via microneurography, compared to men (Hogarth et al., 2007; Ng et al., 1993; Seals & Esler, 2000). Likewise, young women tend to have lower resting AP than young men, and systemic blockade of the sympathetic nervous system decreases AP less in young women (Christou et al., 2005; Schmitt et al., 2010), suggestive of lower tonic sympathetic support of AP. Surprisingly, however, in both young men and women, resting MSNA fails to relate to AP. Recent work by Joyner and colleagues provides insight into this conundrum and also highlights the complex interaction among the factors contributing to resting AP. They found that while MSNA and total peripheral resistance are positively correlated in young men, a negative relationship between resting MSNA and cardiac output minimizes the potential impact of changes in vascular resistance on AP (Charkoudian et al., 2005). Moreover, those men with highest resting MSNA were shown to have the lowest α -adrenergic sensitivity, thus potentially buffering SNA effects on AP (Charkoudian et al., 2005). In contrast, among young women, significant relationships were not observed between MSNA and either cardiac output or total peripheral resistance (Hart et al., 2009). However, following β -adrenergic blockade with propranolol, resting MSNA was positively related to total peripheral resistance and AP (Hart et al., 2011), indicating that β -adrenergic mediated vasodilatation in young women offsets α -adrenergic vasoconstriction (Hart et al., 2011; Kneale et al., 2000). Collectively, these findings emphasize sex-differences in resting MSNA and in the balance between key factors underpinning resting AP in young lean men and women.

Aging increases MSNA in both sexes; however, this effect may be greater in women, particularly after menopause. Indeed, resting MSNA is elevated in postmenopausal women compared to men of the same age (Narkiewicz et al., 2005), and although a positive relationship between MSNA and AP is found in both older men and women, this relationship is much steeper in women. Moreover, unlike in young women, MSNA is

directly related to total peripheral resistance among postmenopausal women, and β -adrenergic blockade is ineffective (Narkiewicz et al., 2005; Hart et al., 2011). Therefore, it is clear that when discerning the influence of obesity on resting MSNA, consideration for underlying age and sex effects is warranted.

The contribution of ovarian hormones to sex differences in basal MSNA has been investigated. MSNA is elevated during the mid-luteal phase (high estrogen and high progesterone concentration), compared to the early follicular phase of the ovarian cycle (low estrogen and progesterone concentration) in young women (Minson et al., 2000). However, no differences in MSNA were noted between the early follicular and late follicular phases (high estrogen and low progesterone concentration) (Ettinger et al., 1998). A recent collaborative effort (Carter et al., 2013) suggests that the increases in MSNA during the mid-luteal phase is due, in part, to the sympathoexcitatory actions of progesterone overcoming the effects of elevations in estrogen favoring sympathoinhibition. Indeed, in postmenopausal women, chronic transdermal estrogen replacement therapy decreased MSNA by ~30% (Vongpatanasin et al., 2001; Weitz et al., 2001). In ovariectomized rats, estrogen administered into central autonomic nuclei, such as the rostral ventrolateral medulla and the nucleus tractus solitarius, produces marked decreases in renal SNA (Saleh et al., 2000). Overall, changes in ovarian hormones are clearly capable of influencing SNA and contribute not only to MSNA variations during the menstrual cycle but also to increases with aging. Thus, the phase of the ovarian cycle and the absolute and relative levels of estrogen and progesterone also need to be considered when assessing resting MSNA in lean and obese pre-menopausal women. In obese postmenopausal women, the use of hormone replacement therapy or lack thereof must be also taken into account.

Sex differences and obesity-induced sympathoexcitation

Several studies have reported increased SNA with human obesity, often as MSNA directly measured using microneurography, but also as organ specific norepinephrine release measured indirectly via the spillover technique [for reviews, see (Davy & Orr, 2009; Smith & Minson, 2012; Lambert et al., 2010b; Esler et al., 2006)]. Elevations in SNA have also been detected in animal models of obesity, beginning soon after a high fat diet has been initiated (Muntzel et al., 2012; Armitage et al., 2012). In both humans and animals, a common theme in the literature is that with obesity, elevations in SNA are tightly related to the level of visceral adiposity (Alvarez et al., 2002; Grassi et al., 2004; Davy & Orr, 2009; Armitage et al., 2012; Muntzel et al., 2012). In contrast, no such relationship has been observed with the degree of subcutaneous obesity in humans, despite its high release of leptin (Alvarez et al., 2004; Grassi et al., 2004).

Thus, conventional wisdom is that visceral obesity is sympathoexcitatory, which can contribute to hypertension development. However, most previous work has primarily included male subjects. This becomes important to consider, because recent studies have reported that the strong relationships between MSNA and waist circumference or BMI found in men are not present in overweight and obese women (Tank et al., 2008; Maqbool et al., 2010; Lambert et al., 2007). One caveat to these studies is that, while the average subject age was ~40 years, postmenopausal women were included in the analyses. Thus, the

variations in SNA and AP control with aging in women described above could have contributed to the failure to observe a correlation between indices of obesity and MSNA in female subjects. However, we have also found that MSNA fails to correlate with either the waist-to-hip ratio or BMI in premenopausal women (Figure 1). Thus, unlike men, obesity does not appear to dictate MSNA in premenopausal women.

Whether a direct relationship between obesity and SNA emerges in postmenopausal women, independently of known age-related increases in SNA, has not been directly investigated. However, studies of primarily older subjects indicate that AP relates to obesity indices, including visceral fat (V-fat) size, in both men and women (Fox et al., 2007; Fujita & Hata, 2014). Given that SNA supports AP in postmenopausal women and contributes to hypertension development (Barnes et al., 2014), these data suggest that such a relationship may become apparent. Regardless, it is clear that more studies documenting the relationship between obesity and MSNA in women as they age are needed.

Another caveat of the studies just described is that they focus on Caucasians. The situation appears to be different in blacks. In contrast to whites, in young black women, but not young black men, the level of SNA is directly related to BMI (Abate et al., 2001). Interestingly, black men have less V-fat compared to white men, and similar amounts compared to black women, yet black women tend to accumulate relatively more fat in the subcutaneous compartment compared to white women (Conway et al., 1995; Despres et al., 2000; Hoffman et al., 2005; Karastergiou et al., 2012; Liu et al., 2014). These data suggest that ethnicity is another factor that must be considered in the context of sex differences and obesity-induced increases in SNA and AP.

The results from animal studies have been more consistent. While no studies have investigated sex differences in the sympathoexcitatory effects of obesity, several have found that consumption of a high fat diet increases adiposity in both males and females, but the obesity increases AP only or sooner in males compared to females (Plut et al., 2002; Roberts et al., 2001; Tamaya-Mori et al., 2002; Gupte et al., 2012). Gonadal steroids may be involved in these sex differences, since estrogen (or the ovaries) protect (Gupte et al., 2012; Roberts et al., 2001), and testosterone amplifies (Tamaya-Mori et al., 2002; Plut et al., 2002), obesity-induced hypertension in animal models of obesity.

Thus, the bulk of the information suggests that the direct association between adiposity and SNA (and AP) present in males may not universally hold for females. The major question addressed in this review is: why? Because so little information is currently available, our primary goal is to provoke further research in this important translational research topic. We consider two possible mechanisms. First, visceral adiposity, leptin, insulin, and angiotensin II have been identified as potential culprits in obesity-induced sympathoexcitation in males [for reviews, see (Esler et al., 2006; Davy & Orr, 2009; Cassis et al., 2008; Hall et al., 2010; Rahmouni, 2010)]. Thus, we explore if these factors wield the same impact in females. Second, given that young or middle-aged women are resistant to vasoconstriction induced by increased SNA, we consider whether sex differences in vascular reactivity to sympathetic activation may contribute.

Sex differences in sympathoexcitatory factors

Adipose tissue

Several recent excellent reviews have detailed the numerous sex differences in the distribution, morphology, and content or activity of adipose tissue (Power & Schulkin, 2008; Richard et al., 2012; Lovejoy & Sainsbury, 2009; Fuente-Martin et al., 2013; Mauvais-Jarvis et al., 2013; Tchernof & Despres, 2013). Chief among these is that adult females accrue more white and brown adipose tissue than males and that, in women compared to men, more white fat is distributed in the subcutaneous compartment (S-fat) relative to the visceral compartment (V-fat). In humans, the risk of cardiovascular disease, including hypertension, is directly correlated to V-fat size, as assessed by waist circumference or more directly via computed tomography (Tchernof & Despres, 2013; Liu et al., 2010; Fox et al., 2007). Not surprisingly, therefore, V-fat exhibits numerous deleterious characteristics, including secretion of inflammatory cytokines, like TNF- α or IL-1, as well as the production and delivery to the liver of adverse metabolites, like nonesterified fatty acids (Tchernof & Despres, 2013; Power & Schulkin, 2008). In young females, therefore, the tendency towards distribution of adipose tissue in the subcutaneous compartment with a more favorable metabolic profile, which is both independent of and facilitated by estrogen (Karastergiou et al., 2012; Mauvais-Jarvis et al., 2013; Tchernof & Despres, 2013), may contribute to the sex differences in obesity-induced sympathoexcitation or hypertension. However, with menopause and the resultant decrease in estrogen levels and redistribution of adipose to the visceral compartment, women may become more vulnerable to obesity-induced increases in SNA and AP. This possibility remains to be directly tested.

In addition to sex differences in the distribution of adipose tissue, white adipocytes from females exhibit other beneficial characteristics compared to males. The cells from females are smaller and are more highly lipogenic and insulin sensitive, due to enhanced insulin-induced signaling and to increased expression of lipid and glucose synthetic proteins (Guerre-Millo et al., 1985; Macotela et al., 2009; Karastergiou et al., 2012). The insulin-sensitizing hormone released from fat, adiponectin, is higher in plasma from females compared to males (Kern et al., 2003; He et al., 2010; Karastergiou et al., 2012). Interestingly, a recent microarray analysis of sex differences in the adipose tissue of diet-induced obese mice confirmed that insulin signaling and lipid synthetic genes are higher in females and also revealed that the expression of inflammatory genes in adipose tissue of obese males is greater than females (Grove et al., 2010). This latter finding is pertinent given recent evidence that obesity induces brain inflammation [for reviews, see (Cai & Liu, 2012; Thaler & Schwartz, 2010; Smith & Minson, 2012)], which can increase SNA and AP (Purkayastha et al., 2011; Felder, 2010). Together, this information suggests that another sex difference that may contribute to the propensity of females to be protected from the sympathoexcitatory effects of obesity may reside in innate differences in adipose tissue composition and responses to increased fat intake. Nevertheless, Grassi et al. (2004) found that a greater sympathetic activation in centrally obese individuals was independent of sex. These findings again highlight the importance of V-fat that when present in females in significant amounts could be an instigator of increased SNA. In agreement, circulating

cytokines such as c-reactive protein and IL-6 are strongly correlated to V-fat accumulation in both men and women (Cartier et al., 2009).

Leptin

Leptin, which is derived largely from S-fat, increases with adiposity, and for a given fat mass, is higher in females compared to males (Power & Schulkin, 2008; Karastergiou et al., 2012). Leptin is well established as a sympathoexcitatory hormone in male animals and humans (Hall et al., 2010; Machleidt et al., 2013; Rahmouni, 2010). However, whether leptin also increases SNA in females was unknown until recently (Shi & Brooks, 2014). Significant evidence indicates that estrogen can enhance the effects of leptin [for reviews, see (Gao & Horvath, 2008; Kelly & Qiu, 2010; Mauvais-Jarvis et al., 2013)], suggesting the potential for exaggerated sympathoexcitatory responses to leptin in females compared to males, in particular during the elevated gonadal steroid segment of the reproductive cycle. In contrast, intracerebroventricular (ICV) leptin does not increase lumbar and renal SNA in rats in diestrus (the low gonadal hormone state); leptin also fails to affect LSNA in ovariectomized rats (Figures 2 and 3). Nevertheless, leptin increased lumbar and renal SNA in rats in proestrus (gonadal hormonal surge) and in ovariectomized rats treated with 17 β -estradiol to increase plasma concentrations to proestrus levels (Figures 2 and 3). Interestingly, leptin-induced increments in splanchnic SNA and HR did not vary with the estrus cycle, indicating that the actions of leptin to increase the activity of various sympathetic nerves and the synergism of leptin with estrogen are mediated via different neuronal pathways or cellular mechanisms. Moreover, the increases in lumbar, renal and splanchnic SNA were similar between proestrus female and male rats (Figure 2), in contrast to the enhanced sensitivity of female rodents to the anorexic effects of leptin (Clegg et al., 2003; Clegg et al., 2006). Therefore, it appears that leptin is incapable of increasing (lumbar and renal) SNA in females without surge rises in estrogen, which may contribute to the failure of MSNA (the correlate of LSNA in rats) or AP in women to relate to indices of obesity (Sheu et al., 1999; Mallamaci et al., 2000; Almeida-Pititto et al., 2006; Lambert et al., 2007; Koh et al., 2008; Allison et al., 2013). A mechanistic explanation for why females in a low estrogen state, unlike males, are resistant to the sympathoexcitatory effects of leptin has not been identified.

The sympathoexcitatory effects of leptin are preserved or exaggerated in obese male animals, despite a blunting of its anorexic effects [for review, see (Mark, 2013)]. While the mechanisms of this “select sensitization” to leptin are unknown, another potential explanation for sex differences in obesity-induced sympathoexcitation may be that these mechanisms are active in males but not in females. Indeed, it is currently unknown if obesity also amplifies the sympathoexcitatory effects of leptin in females as in males.

Insulin

While lean females typically exhibit greater peripheral insulin sensitivity (Mauvais-Jarvis et al., 2013; Sugiyama & Agellon, 2012), central responses to insulin do not appear to be enhanced. Indeed, increases in brain insulin, via ICV infusion in rodents (Clegg et al., 2003) or intranasal administration in humans (Hallschmid et al., 2004; Benedict et al., 2008; Krug et al., 2010), decreases food intake in males, but notably not in females. Moreover, ICV insulin

infusion increases LSNA similarly in both male and female rats and in female rats during diestrus and proestrus (Figure 4) (Shi & Brooks, 2014). Likewise, hyperinsulinemic-euglycemic clamps to increase plasma insulin, while clamping plasma glucose levels at baseline values, increases LSNA in both male and female rats (Cassaglia et al., 2011; Bardgett et al., 2010; Ward et al., 2011) and men and women (Young et al., 2010; Berne et al., 1992; Vollenweider et al., 1994). What remains unclear, however, is whether women respond similarly throughout the reproductive cycle, like rats, as all studies to date have been performed predominantly in men or in women without specific assessment of changes during the menstrual cycle or after menopause.

With obesity, men exhibit a greater tendency to develop insulin resistance and elevated fasting insulin levels than women (Erlingsson et al., 2009; Mauvais-Jarvis et al., 2013). Several studies in humans have tested whether insulin resistant states, like obesity, modify insulin-induced sympathoexcitation; however, no studies have directly assessed sex differences. Vollenweider et al (1994) demonstrated that obese insulin resistant men exhibited attenuated MSNA responses to euglycemic hyperinsulinemia when compared to lean subjects. Similarly, studies of insulin resistant elderly subjects (Fagius et al., 1996) and insulin resistant men or post-menopausal women with metabolic syndrome (Straznicky et al., 2009) have revealed a blunted sympathoexcitatory response to increases in plasma insulin following a glucose load. These findings seem to suggest that, in addition to peripheral resistance to insulin-stimulated glucose uptake, these conditions may also exhibit a central resistance to the sympathoexcitatory actions of insulin.

It must be emphasized, however, that plasma (pancreatic) insulin enters the brain across the blood-brain barrier via a saturable transport mechanism, which is impaired in obesity, specifically in humans (Kaiyala et al., 2000; Banks, 2004; Kern et al., 2006). As a result, access of blood insulin to its central site of action is limited. Moreover, plasma insulin levels and resting MSNA are already elevated in insulin resistant subjects compared to lean counterparts (Vollenweider et al., 1994; Bardgett & Stocker, 2010; Straznicky et al., 2009) and the transport of insulin across the BBB becomes saturated at plasma levels close to normal euglycemic levels, at least in mice (Banks et al., 1997b; Banks et al., 1997a). In support of a similar situation in humans, previous studies demonstrated that a nearly 10-fold dose range of iv insulin produced similar increases in MSNA in lean subjects (Berne et al., 1992; Vollenweider et al., 1994); in rats, a doubling of the iv insulin dose does not double the LSNA response (Morgan et al., 1993). Therefore, as previously discussed (Vollenweider et al., 1994; Limberg et al., 2014), in obese insulin resistant individuals, further elevations in plasma insulin can increase brain insulin levels and thus, SNA, only a limited amount. Thus, additional studies are needed to determine if the central effects of increased plasma insulin levels that accompany obesity-induced insulin resistance produce greater sympathoexcitatory effects. A promising emerging area is the use of intranasal insulin in humans, which bypasses the blood brain barrier, and selectively increases the concentration of insulin in cerebrospinal fluid with minimal absorption into the blood stream (Illum, 2002; Thorne et al., 2004; Hallschmid et al., 2008). This approach may reveal if the central responses to insulin are altered with obesity, and in the context of this review, if sex differences in this response exist in obese or lean humans. Similarly, the sympathoexcitatory responses to ICV insulin infusions have yet to be compared in obese male or female

animals. However, a few studies offer indirect evidence that insulin resistant female rodents may be immune to the hypertensive effects of insulin. First, while a high fructose diet increases plasma insulin levels in both male and female rats, the diet increased AP only in males (Galipeau et al., 2002a). Second, chronic insulin infusion increased systolic pressure in males but not females (Galipeau et al., 2002b). Therefore, another potential explanation for the failure of obesity to uniformly increase SNA in women that requires further investigation is that the central sympathoexcitatory effects of insulin are muted in obese females.

Angiotensin II

Considerable evidence indicates that the renin-angiotensin system (RAS) contributes to obesity-induced sympathoexcitation and hypertension, at least in males. First, obesity in humans and rats increases plasma renin activity (PRA) and angiotensin II (AngII) levels (Dobrian et al., 2000; Gentile et al., 2007; Boustany et al., 2004; Cassis et al., 2008). Second, peripheral blockade of the RAS in obese rodents and human reduces hypertension (Boustany et al., 2005; Dorresteyn et al., 2013; Marinik et al., 2013; Nedogoda et al., 2013; Senador et al., 2009), and hypothalamic knockdown of AT1 receptors lowers systolic blood pressure in obese mice (de Kloet et al., 2013). Finally, treatment of obese humans with RAS inhibitors decreases SNA (Grassi et al., 2003; Amador et al., 2004).

Females are protected from the hypertensive effects of AngII in several animal models [for reviews, see (Sandberg & Ji, 2012; Xue et al., 2013)], and multiple mechanisms may be involved. The RAS includes a hypertensive arm, involving the actions of AngII at AT1 receptors, as well as anti-hypertensive mechanisms, involving the depressor effects of AngII at AT2 receptors and the production, via ACE2, and actions of Ang-(1–7). In the brain, estrogen appears to both up regulate the anti-hypertensive pathway and down regulate the hypertensive pathway (Xue et al., 2013). Likewise, peripherally, females are also able to down regulate the hypertensive pathway, in part by suppressing AT1 receptor expression (Rogers et al., 2007; Wu et al., 2003). Finally, in mice, AngII infusion induces an inflammatory response involving T-cells, which exacerbates hypertension development in males, but not females. (Ji et al., 2014; Pollow et al., 2014).

Given this information, another plausible hypothesis to explain the failure of SNA to correlate with adiposity in females is an attenuation of the levels or actions of the sympathoexcitatory and pressor RAS. In support of this hypothesis, Gupte *et al.* (Gupte et al., 2012) demonstrated that while the increments in body weight and fat mass in female mice on a HFD were greater than in males, AP and plasma AngII levels increased only in males. Moreover, plasma Ang-(1–7) decreased in males, yet it increased in females in association with increased ACE2 activity in adipose tissue (but not kidney). Collectively, this study reemphasizes the importance in females of a shift in the balance away from the hypertensive arm, and towards the antihypertensive arm, of the RAS, in this case in adipose tissue of obese mice. These promising findings warrant further investigation in the context of sex differences and obesity-induced sympathoexcitation.

Sex differences in vascular responses to heightened SNA

Given that obesity increases SNA in males, the next question is whether this sympathoexcitation uniformly translates into vasoconstriction and hypertension development. In both humans and animals, it appears that obesity (before development of metabolic syndrome) simultaneously impairs sympathetically- or α -adrenergic-mediated vasoconstriction (Belin de Chantemele et al., 2011; Jerez et al., 2012; Romanko & Stepp, 2005; Agapitov et al., 2008), which tends to minimize increases in AP. However, increased α -adrenergic sensitivity has been reported in humans once insulin resistance sufficient to increase plasma glucose concentration ensues (Sivitz et al., 2007). Similarly, α -2 mediated forearm vasoconstriction is heightened in insulin resistant metabolic syndrome patients (Limberg et al., 2012). Little definitive consideration, however, has been given to sex differences. As described above, in lean young women, but not young men or postmenopausal women, vascular β -adrenergic receptors counteract α -adrenergic vasoconstriction (Charkoudian & Wallin, 2014). Likewise, in lean rats, sympathoexcitation induced by ICV infusions of leptin or insulin increases AP in males, but not females (Figures 2 and 4). Thus, it may be that increments in SNA in young obese females produce smaller increases in AP. In support, norepinephrine elicits less vasoconstriction in normal and obese women compared to men (Sivitz et al., 2007). Also, in a group of normotensive obese subjects, composed mainly of women, elevated MSNA did not translate into increased sympathetic vasoconstriction in the forearm (Agapitov et al., 2008). Clearly, potential sex differences in the vascular responsiveness to norepinephrine (and other vasoactive factors) in obese subjects as they age warrant additional investigation.

Summary and Conclusions

We have highlighted data suggesting that the sympathoexcitatory and hypertensive consequences of obesity that have been well-established in males may be muted in females. We considered sex differences in the levels and central actions of factors implicated in males to raise SNA and AP as possible explanations for the apparent protection afforded by the female sex. Even in the lean state, sex differences are evident, with females exhibiting less visceral adiposity, lower SNA and SNA-induced vasoconstriction, but higher levels of insulin sensitivity, leptin and adiponectin; the central anorexic responses to insulin and the hypertensive actions of leptin and AngII are reduced in females.

In response to obesity, as summarized in Figure 5A, males compared to females develop greater visceral adiposity with attendant inflammatory cytokine release, elevated levels and actions of the hypertensive arm of the RAS, higher levels of insulin, yet achieve lower levels of leptin. The resulting increases in SNA may translate into greater vasoconstriction (particularly with the advent of hyperglycemia), and hypertension eventually ensues. On the other hand, females may be able to resist obesity-induced hypertension in part due to differences in adipose disposition and its muted inflammatory response and reduced production and actions of pressor RAS components (Figure 5B). Estrogen is clearly a contributor to some (Figure 5B), but not all (e.g. central sympathoexcitatory effects of leptin and insulin), of these sex differences, at least in lean individuals (Mauvais-Jarvis et al., 2013).

Nevertheless, major gaps in our understanding remain. These include whether, with obesity, organ-specific responses to many of the hypertensive contributory factors identified in males prevail in females. For example, are the central sympathoexcitatory effects of insulin, leptin, AngII or cytokines, as well as the responses of the vasculature to sympathetic activation, reduced in obese females? If estrogen is responsible for any aspects of the sex differences in obesity-induced sympathoexcitation or hypertension, which estrogen receptor subtype is involved? As emphasized in a previous review (Lovejoy & Sainsbury, 2009), given the paucity of studies that have included and compared males and females, there is an urgent need for greater study of sex differences, without simply statistically adjusting for sex. Moreover, definitive conclusions on the ability of sex hormones and other mechanisms to modulate sympathetic outflow and its relationship with increased adiposity await further studies that feature the comparisons of males and females and—in females—accounts for changes that may occur within the reproductive cycle as well as after menopause. These studies are critical not only to refine treatment options for obese premenopausal women but also to potentially reveal new therapeutic avenues in obese men and aging women.

Acknowledgments

This work was supported in part by NIH grant HL088552 (vlb) and Grants-in-Aid from the American Heart Association (vlb and pjf); swb was supported by NIH training grant 5T32AR048523-09.

References

- Abate NI, Mansour YH, Tuncel M, Arbique D, Chavoshan B, Kizilbash A, Howell-Stampley T, Vongpatanasin W, Victor RG. Overweight and sympathetic overactivity in black Americans. *Hypertension*. 2001; 38:379–383. [PubMed: 11566908]
- Agapitov AV, Correia ML, Sinkey CA, Haynes WG. Dissociation between sympathetic nerve traffic and sympathetically mediated vascular tone in normotensive human obesity. *Hypertension*. 2008; 52:687–695. [PubMed: 18695151]
- Allison MA, Ix JH, Morgan C, McClelland RL, Rifkin D, Shimbo D, Criqui MH. Higher leptin is associated with hypertension: the Multi-Ethnic Study of Atherosclerosis. *J Hum Hypertens*. 2013; 27:617–622. [PubMed: 23535989]
- Almeida-Pititto B, Gimeno SG, Freire RD, Ribeiro-Filho FF, Ferreira SR. Leptin is not associated independently with hypertension in Japanese-Brazilian women. *Braz J Med Biol Res*. 2006; 39:99–105. [PubMed: 16400470]
- Alvarez GE, Ballard TP, Beske SD, Davy KP. Subcutaneous obesity is not associated with sympathetic neural activation. *Am J Physiol Heart Circ Physiol*. 2004; 287:H414–H418. [PubMed: 14988078]
- Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activation in visceral obesity. *Circulation*. 2002; 106:2533–2536. [PubMed: 12427647]
- Amador N, Guizar JM, Malacara JM, Perez-Luque E, Paniagua R. Sympathetic activity and response to ACE inhibitor (enalapril) in normotensive obese and non-obese subjects. *Arch Med Res*. 2004; 35:54–58. [PubMed: 15036801]
- Armitage JA, Burke SL, Prior LJ, Barzel B, Eikelis N, Lim K, Head GA. Rapid onset of renal sympathetic nerve activation in rabbits fed a high-fat diet. *Hypertension*. 2012; 60:163–171. [PubMed: 22647890]
- Banks WA. The source of cerebral insulin. *European Journal of Pharmacology*. 2004; 490:5–12. [PubMed: 15094069]
- Banks WA, Jaspan JB, Huang W, Kastin AJ. Transport of insulin across the blood-brain barrier: saturability at euglycemic doses of insulin. *Peptides*. 1997a; 18:1423–1429. [PubMed: 9392846]

- Banks WA, Jaspan JB, Kastin AJ. Selective, physiological transport of insulin across the blood-brain barrier: novel demonstration by species-specific radioimmunoassays. *Peptides*. 1997b; 18:1257–1262. [PubMed: 9396070]
- Bardgett ME, McCarthy JJ, Stocker SD. Glutamatergic receptor activation in the rostral ventrolateral medulla mediates the sympathoexcitatory response to hyperinsulinemia. *Hypertension*. 2010; 55:284–290. [PubMed: 20065145]
- Bardgett ME, Stocker SD. Diet-Induced obesity causes selective insulin resistance. *FASEB J*. 2010; 24:809.23.
- Barnes JN, Hart EC, Curry TB, Nicholson WT, Eisenach JH, Wallin BG, Charkoudian N, Joyner MJ. Aging enhances autonomic support of blood pressure in women. *Hypertension*. 2014; 63:303–308. [PubMed: 24324040]
- Belin de Chantemele EJ, Mintz JD, Rainey WE, Stepp DW. Impact of leptin-mediated sympatho-activation on cardiovascular function in obese mice. *Hypertension*. 2011; 58:271–279. [PubMed: 21690486]
- Benedict C, Kern W, Schultes B, Born J, Hallschmid M. Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. *J Clin Endocrinol Metab*. 2008; 93:1339–1344. [PubMed: 18230654]
- Berne C, Fagius J, Pollare T, Hjemdahl P. The sympathetic response to euglycaemic hyperinsulinaemia. Evidence from microelectrode nerve recordings in healthy subjects. *Diabetologia*. 1992; 35:873–879. [PubMed: 1397783]
- Boustany CM, Bharadwaj K, Daugherty A, Brown DR, Randall DC, Cassis LA. Activation of the systemic and adipose renin-angiotensin system in rats with diet-induced obesity and hypertension. *Am J Physiol Regul Integr Comp Physiol*. 2004; 287:R943–R949. [PubMed: 15191907]
- Boustany CM, Brown DR, Randall DC, Cassis LA. AT1-receptor antagonism reverses the blood pressure elevation associated with diet-induced obesity. *Am J Physiol Regul Integr Comp Physiol*. 2005; 289:R181–R186. [PubMed: 15774768]
- Cai D, Liu T. Inflammatory cause of metabolic syndrome via brain stress and NF-kappaB. *Aging* (Albany NY). 2012; 4:98–115. [PubMed: 22328600]
- Carter JR, Fu Q, Minson CT, Joyner MJ. Ovarian cycle and sympathoexcitation in premenopausal women. *Hypertension*. 2013; 61:395–399. [PubMed: 23172932]
- Cartier A, Cote M, Lemieux I, Perusse L, Tremblay A, Bouchard C, Despres JP. Sex differences in inflammatory markers: what is the contribution of visceral adiposity? *Am J Clin Nutr*. 2009; 89:1307–1314. [PubMed: 19297456]
- Cassaglia PA, Hermes SM, Aicher SA, Brooks VL. Insulin acts in the arcuate nucleus to increase lumbar sympathetic nerve activity and baroreflex function in rats. *J Physiol*. 2011; 589:1643–1662. [PubMed: 21300750]
- Cassis LA, Police SB, Yiannikouris F, Thatcher SE. Local adipose tissue renin-angiotensin system. *Curr Hypertens Rep*. 2008; 10:93–98. [PubMed: 18474174]
- Charkoudian N, Joyner MJ, Johnson CP, Eisenach JH, Dietz NM, Wallin BG. Balance between cardiac output and sympathetic nerve activity in resting humans: role in arterial pressure regulation. *J Physiol*. 2005; 568:315–321. [PubMed: 16037092]
- Charkoudian N, Wallin BG. Sympathetic neural activity to the cardiovascular system: integrator of systemic physiology and interindividual characteristics. *Compr Physiol*. 2014; 4:825–850. [PubMed: 24715570]
- Christou DD, Jones PP, Jordan J, Diedrich A, Robertson D, Seals DR. Women have lower tonic autonomic support of arterial blood pressure and less effective baroreflex buffering than men. *Circulation*. 2005; 111:494–498. [PubMed: 15687139]
- Clegg DJ, Brown LM, Woods SC, Benoit SC. Gonadal hormones determine sensitivity to central leptin and insulin. *Diabetes*. 2006; 55:978–987. [PubMed: 16567519]
- Clegg DJ, Riedy CA, Smith KA, Benoit SC, Woods SC. Differential sensitivity to central leptin and insulin in male and female rats. *Diabetes*. 2003; 52:682–687. [PubMed: 12606509]
- Conway JM, Yanovski SZ, Avila NA, Hubbard VS. Visceral adipose tissue differences in black and white women. *Am J Clin Nutr*. 1995; 61:765–771. [PubMed: 7702017]

- Davy KP, Orr JS. Sympathetic nervous system behavior in human obesity. *Neurosci Biobehav Rev*. 2009; 33:116–124. [PubMed: 18602694]
- de Kloet AD, Pati D, Wang L, Hiller H, Sumners C, Frazier CJ, Seeley RJ, Herman JP, Woods SC, Krause EG. Angiotensin type 1a receptors in the paraventricular nucleus of the hypothalamus protect against diet-induced obesity. *Journal of Neuroscience*. 2013; 33:4825–4833. [PubMed: 23486953]
- Despres JP, Couillard C, Gagnon J, Bergeron J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Bouchard C. Race, visceral adipose tissue, plasma lipids, and lipoprotein lipase activity in men and women: the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) family study. *Arterioscler Thromb Vasc Biol*. 2000; 20:1932–1938. [PubMed: 10938014]
- Dobrian AD, Davies MJ, Prewitt RL, Lauterio TJ. Development of hypertension in a rat model of diet-induced obesity. *Hypertension*. 2000; 35:1009–1015. [PubMed: 10775577]
- Dorresteijn JA, Schrover IM, Visseren FL, Scheffer PG, Oey PL, Danser AH, Spiering W. Differential effects of renin-angiotensin-aldosterone system inhibition, sympathoinhibition and diuretic therapy on endothelial function and blood pressure in obesity-related hypertension: a double-blind, placebo-controlled cross-over trial. *J Hypertens*. 2013; 31:393–403. [PubMed: 23235355]
- Erlingsson S, Herard S, Dahlqvist LO, Lindstrom T, Lanne T, Borga M, Nystrom FH. Men develop more intraabdominal obesity and signs of the metabolic syndrome after hyperalimentation than women. *Metabolism*. 2009; 58:995–1001. [PubMed: 19394660]
- Esler M, Straznicky N, Eikelis N, Masuo K, Lambert G, Lambert E. Mechanisms of sympathetic activation in obesity-related hypertension. *Hypertension*. 2006; 48:787–796. [PubMed: 17000932]
- Ettinger SM, Silber DH, Gray KS, Smith MB, Yang QX, Kunselman AR, Sinoway LI. Effects of the ovarian cycle on sympathetic neural outflow during static exercise. *J Appl Physiol* (1985). 1998; 85:2075–2081. [PubMed: 9843528]
- Fagius J, Ellerfelt K, Lithell H, Berne C. Increase in muscle nerve sympathetic activity after glucose intake is blunted in the elderly. *Clin Auton Res*. 1996; 6:195–203. [PubMed: 8902315]
- Felder RB. Mineralocorticoid receptors, inflammation and sympathetic drive in a rat model of systolic heart failure. *Exp Physiol*. 2010; 95:19–25. [PubMed: 19648480]
- Fisher JP, Young CN, Fadel PJ. Central sympathetic overactivity: maladies and mechanisms. *Auton Neurosci*. 2009; 148:5–15. [PubMed: 19268634]
- Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino RB Sr, O'Donnell CJ. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation*. 2007; 116:39–48. [PubMed: 17576866]
- Fuente-Martin E, Garcia-Caceres C, Morselli E, Clegg DJ, Chowen JA, Finan B, Brinton RD, Tschop MH. Estrogen, astrocytes and the neuroendocrine control of metabolism. *Rev Endocr Metab Disord*. 2013; 14:331–338. [PubMed: 24009071]
- Fujita M, Hata A. Sex and age differences in the effect of obesity on incidence of hypertension in the Japanese population: A large historical cohort study. *J Am Soc Hypertens*. 2014; 8:64–70. [PubMed: 24113321]
- Galipeau D, Verma S, McNeill JH. Female rats are protected against fructose-induced changes in metabolism and blood pressure. *Am J Physiol Heart Circ Physiol*. 2002a; 283:H2478–H2484. [PubMed: 12427595]
- Galipeau DM, Yao L, McNeill JH. Relationship among hyperinsulinemia, insulin resistance, and hypertension is dependent on sex. *Am J Physiol Heart Circ Physiol*. 2002b; 283:H562–H567. [PubMed: 12124202]
- Gao Q, Horvath TL. Cross-talk between estrogen and leptin signaling in the hypothalamus. *Am J Physiol Endocrinol Metab*. 2008; 294:E817–E826. [PubMed: 18334610]
- Gentile CL, Orr JS, Davy BM, Davy KP. Modest weight gain is associated with sympathetic neural activation in nonobese humans. *Am J Physiol Regul Integr Comp Physiol*. 2007; 292:R1834–R1838. [PubMed: 17218435]
- Grassi G, Dell'Oro R, Facchini A, Quarti TF, Bolla GB, Mancia G. Effect of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensives. *J Hypertens*. 2004; 22:2363–2369. [PubMed: 15614031]

- Grassi G, Seravalle G, Dell'Oro R, Trevano FQ, Bombelli M, Scopelliti F, Facchini A, Mancia G. Comparative effects of candesartan and hydrochlorothiazide on blood pressure, insulin sensitivity, and sympathetic drive in obese hypertensive individuals: results of the CROSS study. *J Hypertens*. 2003; 21:1761–1769. [PubMed: 12923410]
- Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. *Int J Obes (Lond)*. 2010; 34:989–1000. [PubMed: 20157318]
- Guerre-Millo M, Leturque A, Girard J, Lavau M. Increased insulin sensitivity and responsiveness of glucose metabolism in adipocytes from female versus male rats. *J Clin Invest*. 1985; 76:109–116. [PubMed: 3894416]
- Gupte M, Thatcher SE, Boustany-Kari CM, Shoemaker R, Yiannikouris F, Zhang X, Karounos M, Cassis LA. Angiotensin converting enzyme 2 contributes to sex differences in the development of obesity hypertension in C57BL/6 mice. *Arterioscler Thromb Vasc Biol*. 2012; 32:1392–1399. [PubMed: 22460555]
- Hall JE, da Silva AA, do Carmo JM, Dubinion J, Hamza S, Munusamy S, Smith G, Stec DE. Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins. *J Biol Chem*. 2010; 285:17271–17276. [PubMed: 20348094]
- Hallschmid M, Benedict C, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin reduces body fat in men but not in women. *Diabetes*. 2004; 53:3024–3029. [PubMed: 15504987]
- Hallschmid M, Benedict C, Schultes B, Perras B, Fehm HL, Kern W, Born J. Towards the therapeutic use of intranasal neuropeptide administration in metabolic and cognitive disorders. *Regul Pept*. 2008; 149:79–83. [PubMed: 18442862]
- Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach J, Joyner MJ. Sex and ageing differences in resting arterial pressure regulation: the role of the beta-adrenergic receptors. *J Physiol*. 2011; 589:5285–5297. [PubMed: 21859824]
- Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach JH, Joyner MJ. Sex differences in sympathetic neural-hemodynamic balance: implications for human blood pressure regulation. *Hypertension*. 2009; 53:571–576. [PubMed: 19171792]
- He H, Ni Y, Chen J, Zhao Z, Zhong J, Liu D, Yan Z, Zhang W, Zhu Z. Sex difference in cardiometabolic risk profile and adiponectin expression in subjects with visceral fat obesity. *Transl Res*. 2010; 155:71–77. [PubMed: 20129487]
- Hoffman DJ, Wang Z, Gallagher D, Heymsfield SB. Comparison of visceral adipose tissue mass in adult African Americans and whites. *Obes Res*. 2005; 13:66–74. [PubMed: 15761164]
- Hogarth AJ, Mackintosh AF, Mary DA. Gender-related differences in the sympathetic vasoconstrictor drive of normal subjects. *Clin Sci (Lond)*. 2007; 112:353–361. [PubMed: 17129210]
- Illum L. Nasal drug delivery: new developments and strategies. *Drug Discov Today*. 2002; 7:1184–1189. [PubMed: 12547019]
- Jerez S, Scacchi F, Sierra L, Karbinder S, de Bruno MP. Vascular hyporeactivity to angiotensin II and noradrenaline in a rabbit model of obesity. *Journal of Cardiovascular Pharmacology*. 2012; 59:49–57. [PubMed: 21921805]
- Ji H, Zheng W, Li X, Liu J, Wu X, Zhang MA, Umans JG, Hay M, Speth RC, Dunn SE, Sandberg K. Sex-Specific T-Cell Regulation of Angiotensin II-Dependent Hypertension. *Hypertension*. 2014
- Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW. Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. *Diabetes*. 2000; 49:1525–1533. [PubMed: 10969837]
- Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. *Biol Sex Differ*. 2012; 3:13. [PubMed: 22651247]
- Kelly MJ, Qiu J. Estrogen signaling in hypothalamic circuits controlling reproduction. *Brain Research*. 2010; 1364:44–52. [PubMed: 20807512]
- Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor- α expression. *Diabetes*. 2003; 52:1779–1785. [PubMed: 12829646]

- Kern W, Benedict C, Schultes B, Plohr F, Moser A, Born J, Fehm HL, Hallschmid M. Low cerebrospinal fluid insulin levels in obese humans. *Diabetologia*. 2006; 49:2790–2792. [PubMed: 16951936]
- Kneale BJ, Chowieńczyk PJ, Brett SE, Coltart DJ, Ritter JM. Gender differences in sensitivity to adrenergic agonists of forearm resistance vasculature. *Journal of the American College of Cardiology*. 2000; 36:1233–1238. [PubMed: 11028476]
- Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. *Circulation*. 2008; 117:3238–3249. [PubMed: 18574061]
- Krug R, Benedict C, Born J, Hallschmid M. Comparable sensitivity of postmenopausal and young women to the effects of intranasal insulin on food intake and working memory. *J Clin Endocrinol Metab*. 2010; 95:E468–E472. [PubMed: 20719831]
- Lambert E, Sari CI, Dawood T, Nguyen J, McGrane M, Eikelis N, Chopra R, Wong C, Chatzivlastou K, Head G, Straznicki N, Esler M, Schlaich M, Lambert G. Sympathetic nervous system activity is associated with obesity-induced subclinical organ damage in young adults. *Hypertension*. 2010a; 56:351–358. [PubMed: 20625075]
- Lambert E, Straznicki N, Eikelis N, Esler M, Dawood T, Masuo K, Schlaich M, Lambert G. Gender differences in sympathetic nervous activity: influence of body mass and blood pressure. *J Hypertens*. 2007; 25:1411–1419. [PubMed: 17563563]
- Lambert GW, Straznicki NE, Lambert EA, Dixon JB, Schlaich MP. Sympathetic nervous activation in obesity and the metabolic syndrome—causes, consequences and therapeutic implications. *Pharmacol Ther*. 2010b; 126:159–172. [PubMed: 20171982]
- Limberg JK, Curry TB, Prabhakar NR, Joyner MJ. Is insulin the new intermittent hypoxia? *Med Hypotheses*. 2014; 82:730–735. [PubMed: 24690299]
- Limberg JK, Morgan BJ, Sebranek JJ, Proctor LT, Walker BJ, Eldridge MW, Schrage WG. Altered neurovascular control of the resting circulation in human metabolic syndrome. *J Physiol*. 2012; 590:6109–6119. [PubMed: 23027821]
- Liu J, Coady S, Carr JJ, Hoffmann U, Taylor HA, Fox CS. Differential associations of abdominal visceral, subcutaneous adipose tissue with cardiometabolic risk factors between African and European Americans. *Obesity (Silver Spring)*. 2014; 22:811–818. [PubMed: 23408700]
- Liu J, Fox CS, Hickson DA, May WD, Hairston KG, Carr JJ, Taylor HA. Impact of abdominal visceral and subcutaneous adipose tissue on cardiometabolic risk factors: the Jackson Heart Study. *J Clin Endocrinol Metab*. 2010; 95:5419–5426. [PubMed: 20843952]
- Lovejoy JC, Sainsbury A. Sex differences in obesity and the regulation of energy homeostasis. *Obes Rev*. 2009; 10:154–167. [PubMed: 19021872]
- Machleidt F, Simon P, Krapalis AF, Hallschmid M, Lehnert H, Sayk F. Experimental hyperleptinemia acutely increases vasoconstrictory sympathetic nerve activity in healthy humans. *J Clin Endocrinol Metab*. 2013; 98:E491–E496. [PubMed: 23393176]
- Macotela Y, Boucher J, Tran TT, Kahn CR. Sex and depot differences in adipocyte insulin sensitivity and glucose metabolism. *Diabetes*. 2009; 58:803–812. [PubMed: 19136652]
- Mallamaci F, Cuzzola F, Tripepi G, Cutrupi S, Parlongo S, Tripepi R, Zoccali C. Gender-dependent differences in plasma leptin in essential hypertension. *Am J Hypertens*. 2000; 13:914–920. [PubMed: 10950400]
- Maqbool A, West RM, Galloway SL, Drinkhill MJ, Mary DA, Greenwood JP, Ball SG. Resting sympathetic nerve activity is related to age, sex and arterial pressure but not to alpha2-adrenergic receptor subtype. *J Hypertens*. 2010; 28:2084–2093. [PubMed: 20613626]
- Marinik EL, Frisard MI, Hulver MW, Davy BM, Rivero JM, Savla JS, Davy KP. Angiotensin II receptor blockade and insulin sensitivity in overweight and obese adults with elevated blood pressure. *Ther Adv Cardiovasc Dis*. 2013; 7:11–20. [PubMed: 23328189]
- Mark AL. Selective leptin resistance revisited. *Am J Physiol Regul Integr Comp Physiol*. 2013; 305:R566–R581. [PubMed: 23883674]
- Mauvais-Jarvis F, Clegg DJ, Hevener AL. The role of estrogens in control of energy balance and glucose homeostasis. *Endocrine Reviews*. 2013; 34:309–338. [PubMed: 23460719]

- Minson CT, Halliwill JR, Young TM, Joyner MJ. Influence of the menstrual cycle on sympathetic activity, baroreflex sensitivity, and vascular transduction in young women. *Circulation*. 2000; 101:862–868. [PubMed: 10694525]
- Morgan DA, Balon TW, Ginsberg BH, Mark AL. Nonuniform regional sympathetic nerve responses to hyperinsulinemia in rats. *Am J Physiol*. 1993; 264:R423–R427. [PubMed: 8447499]
- Muntzel MS, Al Naimi OA, Barclay A, Ajasin D. Cafeteria diet increases fat mass and chronically elevates lumbar sympathetic nerve activity in rats. *Hypertension*. 2012; 60:1498–1502. [PubMed: 23090774]
- Narkiewicz K, Phillips BG, Kato M, Hering D, Bieniaszewski L, Somers VK. Gender-selective interaction between aging, blood pressure, and sympathetic nerve activity. *Hypertension*. 2005; 45:522–525. [PubMed: 15767469]
- Nedogoda SV, Ledyayeva AA, Chumachok EV, Tsoma VV, Mazina G, Salasyuk AS, Barykina IN. Randomized trial of perindopril, enalapril, losartan and telmisartan in overweight or obese patients with hypertension. *Clin Drug Investig*. 2013; 33:553–561.
- Ng AV, Callister R, Johnson DG, Seals DR. Age and gender influence muscle sympathetic nerve activity at rest in healthy humans. *Hypertension*. 1993; 21:498–503. [PubMed: 8458648]
- Plut C, Ribiere C, Giudicelli Y, Dausse JP. Gender differences in hypothalamic tyrosine hydroxylase and alpha(2)-adrenoceptor subtype gene expression in cafeteria diet-induced hypertension and consequences of neonatal androgenization. *Journal of Pharmacology and Experimental Therapeutics*. 2002; 302:525–531. [PubMed: 12130711]
- Pollow DP, Uhrlaub J, Romero-Aleshire MJ, Sandberg K, Nikolich-Zugich J, Brooks HL, Hay M. Sex Differences in T-Lymphocyte Tissue Infiltration and Development of Angiotensin II Hypertension. *Hypertension*. 2014
- Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr*. 2008; 99:931–940. [PubMed: 17977473]
- Purkayastha S, Zhang G, Cai D. Uncoupling the mechanisms of obesity and hypertension by targeting hypothalamic IKK-beta and NF-kappaB. *Nat Med*. 2011; 17:883–887. [PubMed: 21642978]
- Rahmouni K. Leptin-Induced Sympathetic Nerve Activation: Signaling Mechanisms and Cardiovascular Consequences in Obesity. *Curr Hypertens Rev*. 2010; 6:104–209. [PubMed: 21562617]
- Richard D, Monge-Roffarello B, Chechi K, Labbe SM, Turcotte EE. Control and physiological determinants of sympathetically mediated brown adipose tissue thermogenesis. *Front Endocrinol (Lausanne)*. 2012; 3:36. [PubMed: 22654862]
- Roberts CK, Vaziri ND, Barnard RJ. Protective effects of estrogen on gender-specific development of diet-induced hypertension. *J Appl Physiol* (1985). 2001; 91:2005–2009. [PubMed: 11641337]
- Rogers JL, Mitchell AR, Maric C, Sandberg K, Myers A, Mulroney SE. Effect of sex hormones on renal estrogen and angiotensin type 1 receptors in female and male rats. *Am J Physiol Regul Integr Comp Physiol*. 2007; 292:R794–R799. [PubMed: 16990489]
- Romanko OP, Stepp DW. Reduced constrictor reactivity balances impaired vasodilation in the mesenteric circulation of the obese Zucker rat. *Am J Physiol Heart Circ Physiol*. 2005; 289:H2097–H2102. [PubMed: 15951349]
- Saleh MC, Connell BJ, Saleh TM. Autonomic and cardiovascular reflex responses to central estrogen injection in ovariectomized female rats. *Brain Research*. 2000; 879:105–114. [PubMed: 11011011]
- Sandberg K, Ji H. Sex differences in primary hypertension. *Biol Sex Differ*. 2012; 3:7. [PubMed: 22417477]
- Schlaich MP, Grassi G, Lambert GW, Straznicki N, Esler MD, Dixon J, Lambert EA, Redon J, Narkiewicz K, Jordan J. European Society of Hypertension Working Group on Obesity Obesity-induced hypertension and target organ damage: current knowledge and future directions. *J Hypertens*. 2009; 27:207–211. [PubMed: 19155773]
- Schmitt JA, Joyner MJ, Charkoudian N, Wallin BG, Hart EC. Sex differences in alpha-adrenergic support of blood pressure. *Clin Auton Res*. 2010; 20:271–275. [PubMed: 20221842]
- Seals DR, Esler MD. Human ageing and the sympathoadrenal system. *J Physiol*. 2000; 528:407–417. [PubMed: 11060120]

- Senador D, Kanakamedala K, Irigoyen MC, Morris M, Elased KM. Cardiovascular and autonomic phenotype of db/db diabetic mice. *Exp Physiol*. 2009; 94:648–658. [PubMed: 19218356]
- Sheu WH, Lee WJ, Chen YT. High plasma leptin concentrations in hypertensive men but not in hypertensive women. *J Hypertens*. 1999; 17:1289–1295. [PubMed: 10489106]
- Shi Z, Brooks VL. Leptin differentially increases sympathetic nerve activity and its baroreflex regulation in female rats: role of estrogen. *J Physiol*. 2014
- Sivitz WI, Wayson SM, Bayless ML, Sinkey CA, Haynes WG. Obesity impairs vascular relaxation in human subjects: hyperglycemia exaggerates adrenergic vasoconstriction arterial dysfunction in obesity and diabetes. *J Diabetes Complications*. 2007; 21:149–157. [PubMed: 17493547]
- Smith MM, Minson CT. Obesity and adipokines: effects on sympathetic overactivity. *J Physiol*. 2012; 590:1787–1801. [PubMed: 22351630]
- Straznicki NE, Lambert GW, Masuo K, Dawood T, Eikelis N, Nestel PJ, McGrane MT, Mariani JA, Socratous F, Chopra R, Esler MD, Schlaich MP, Lambert EA. Blunted sympathetic neural response to oral glucose in obese subjects with the insulin-resistant metabolic syndrome. *Am J Clin Nutr*. 2009; 89:27–36. [PubMed: 19056585]
- Sugiyama MG, Agellon LB. Sex differences in lipid metabolism and metabolic disease risk. *Biochem Cell Biol*. 2012; 90:124–141. [PubMed: 22221155]
- Tamaya-Mori N, Uemura K, Iguchi A. Gender differences in the dietary lard-induced increase in blood pressure in rats. *Hypertension*. 2002; 39:1015–1020. [PubMed: 12019285]
- Tank J, Heusser K, Diedrich A, Hering D, Luft FC, Busjahn A, Narkiewicz K, Jordan J. Influences of gender on the interaction between sympathetic nerve traffic and central adiposity. *J Clin Endocrinol Metab*. 2008; 93:4974–4978. [PubMed: 18782878]
- Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev*. 2013; 93:359–404. [PubMed: 23303913]
- Thaler JP, Schwartz MW. Minireview: Inflammation and obesity pathogenesis: the hypothalamus heats up. *Endocrinology*. 2010; 151:4109–4115. [PubMed: 20573720]
- Thorne RG, Pronk GJ, Padmanabhan V, Frey WH. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience*. 2004; 127:481–496. [PubMed: 15262337]
- Vollenweider P, Randin D, Tappy L, Jequier E, Nicod P, Scherrer U. Impaired insulin-induced sympathetic neural activation and vasodilation in skeletal muscle in obese humans. *J Clin Invest*. 1994; 93:2365–2371. [PubMed: 8200969]
- Vongpatanasin W, Tuncel M, Mansour Y, Arbiq D, Victor RG. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation*. 2001; 103:2903–2908. [PubMed: 11413078]
- Ward KR, Bardgett JF, Wolfgang L, Stocker SD. Sympathetic response to insulin is mediated by melanocortin 3/4 receptors in the hypothalamic paraventricular nucleus. *Hypertension*. 2011; 57:435–441. [PubMed: 21263116]
- Weitz G, Elam M, Born J, Fehm HL, Dodt C. Postmenopausal estrogen administration suppresses muscle sympathetic nerve activity. *J Clin Endocrinol Metab*. 2001; 86:344–348. [PubMed: 11232022]
- Wu Z, Maric C, Roesch DM, Zheng W, Verbalis JG, Sandberg K. Estrogen regulates adrenal angiotensin AT1 receptors by modulating AT1 receptor translation. *Endocrinology*. 2003; 144:3251–3261. [PubMed: 12810582]
- Xue B, Johnson AK, Hay M. Sex differences in angiotensin II- and aldosterone-induced hypertension: the central protective effects of estrogen. *Am J Physiol Regul Integr Comp Physiol*. 2013; 305:R459–R463. [PubMed: 23883676]
- Young CN, Deo SH, Chaudhary K, Thyfault JP, Fadel PJ. Insulin enhances the gain of arterial baroreflex control of muscle sympathetic nerve activity in humans. *J Physiol*. 2010; 588:3593–3603. [PubMed: 20643774]

Highlights

- Obesity increases sympathetic nerve activity more in males compared to females.
- The mechanisms for this sex difference are unknown.
- We examine several possible mechanisms.
- These include sex differences in visceral fat and key regulatory hormones.
- Overall, there is an urgent need for further study.

Figure 1. MSNA does not correlate with adiposity in women

Linear regression analysis demonstrating lack of relationship between resting MSNA and waist-hip ratio (Panel A) and BMI (Panel B) in healthy premenopausal women (n=23, age: 35±3 yrs). Retrospective data analysis of microneurographic recordings from Fadel laboratory.

Figure 2. Comparison of leptin's effects in male and female rats

A, ICV leptin increased MAP in male rats (n=16), but not in female rats during diestrus (n=15) or proestrus (n=14). **B**, The basal HR of male rats is lower than that of female rats. ICV leptin increased HR in both male (n=16) and female rats (n=15, diestrus; n=14, proestrus). **C**, ICV leptin increased LSNA in male rats (n=5) and female proestrus rats (n=6), but not in females in diestrus (n=6); **D**, ICV leptin increased RSNA in male rats (n=5) and females in proestrus (n=4), but not in females in diestrus (n=4). **E**, ICV leptin increased

splanchnic SNA (SSNA) in male rats (n=6) and female rats (n=5, diestrus; n=4, proestrus). * $P < 0.05$ vs control ; † $P < 0.05$ between groups. Data from (Shi & Brooks, 2014).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 3. Leptin increases LSNA and HR in E2-treated ovariectomized (OVX) rats, but not in OVX rats

A, ICV leptin did not alter MAP in OVX rats (n=5) or in E2-treated OVX rats (OVX-E2, n=4). However, ICV leptin increased HR (B) and LSNA (C) in E2-treated OVX rats (n=4), but not in OVX rats (n = 5). * $P < 0.05$ vs control; † $P < 0.05$ between groups. Data from (Shi & Brooks, 2014)

Figure 4. Comparison of insulin's effects on MAP, LSNA and HR in male and female rats
A, ICV insulin increased MAP in male rats (n=5), but not in female rats in proestrus (n=5) and diestrus (n=5). However, ICV insulin increased HR (**B**) and LSNA (**C**) similarly in male (n=5), female proestrus (n=5) and diestrus rats (n=5). * P < 0.05 vs control. Data from (Shi & Brooks, 2014).

Figure 5. Summary

General schematic depicting some factors that may explain the lesser propensity for obese females (B) to exhibit elevated SNA and AP compared to obese males (A). In females, potential inhibitory and facilitatory effects of 17 β -estradiol (E2) are indicated by minus (–) and plus (+) symbols, respectively. See text for details.