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Obesity-induced increases in sympathetic nerve activity: Sex matters

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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.

1 . 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 and Orr, 2009; Esler et al., 2006; G.W. Lambert et al., 2010]. Moreover, elevated SNA may accelerate the progression of end organ damage (vascular, metabolic, cardiac, renal), independently of any rise in arterial pressure (AP) (E. Lambert et al., 2010; 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 has 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.

2 . 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 and 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

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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 concentrations), compared to the early follicular phase of the ovarian cycle (low estrogen and progesterone concentrations) 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 concentrations) (Ettinger et al., 1998). A recent collaborative effort (Carter et al., 2013) suggests that the increases in MSNA during the mid-luteal phase are 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 the 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 premenopausal women. In obese postmenopausal women, the use of hormone replacement therapy or lack thereof must be also taken into account.

3 . 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 and Orr, 2009; Smith and Minson, 2012; G.W. Lambert et al., 2010; 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 and 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 (Fig. 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 and 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.,

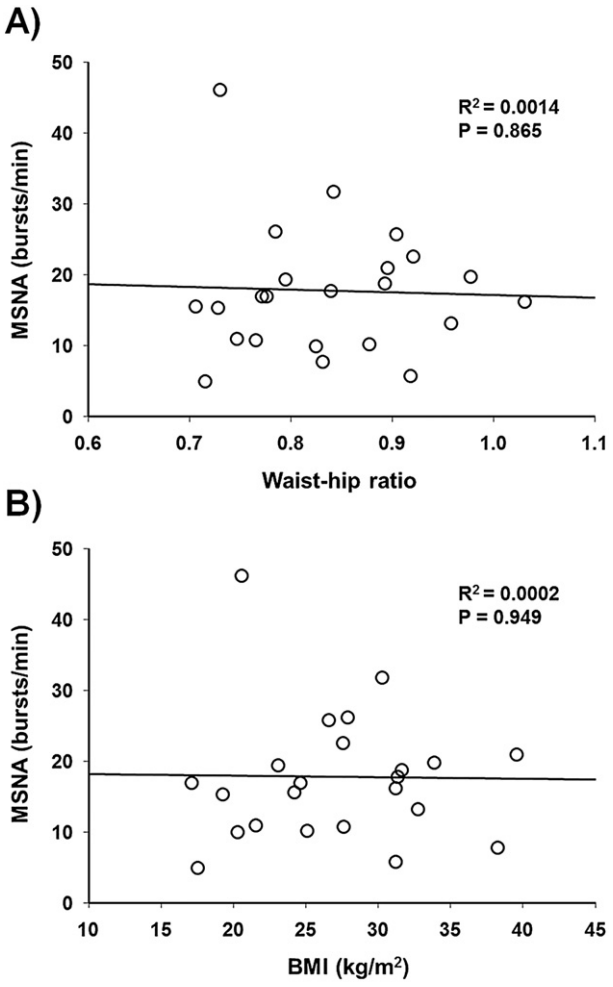

Fig. 1. MSNA does not correlate with adiposity in women. Linear regression analysis demonstrating lack of relationship between resting MSNA and waist–hip ratio (Panel A) and BMI (Panel B) in healthy premenopausal women (n = 23, age: 35 ± 3 years). Retrospective data analysis of microneurographic recordings from Fadel laboratory.