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Sex differences in α-adrenergic support of blood pressure

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Abstract

We tested whether the inter-individual variability in α-adrenergic support of blood pressure plays a critical role in the sex differences in tonic support of blood pressure by the autonomic nervous system. Blockade of the α-adrenergic receptors was achieved via phentolamine and showed a smaller ($P < 0.05$) decrease in blood pressure in women compared to men, implying that α-adrenergic support of blood pressure is less in women than in men.

Keywords

Sex differences; α-Adrenergic; Blood pressure

Introduction

The autonomic nervous system (ANS) plays a crucial role in the tonic maintenance of blood pressure (BP). For example, muscle sympathetic nerve activity (MSNA) is tightly coupled to BP via the baroreflex [1]. Additionally, it has been known for decades that MSNA among normotensive individuals of both sexes can vary greatly, despite similar levels of resting BP [2,3]. Recently Charkoudian et al. [4] investigated this paradox and showed that BP in young men is regulated by a balance between cardiac output (CO) [4] and sympathetic neural control of peripheral resistance [4–7]. Therefore, in men, a high level of MSNA and total peripheral resistance (TPR) is balanced by a lower CO and decreased vasoconstrictor responsiveness to adrenergic stimuli in men. Unexpectedly, in women, MSNA is not related to TPR or CO [8], indicating that women regulate BP differently in comparison to young men.

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Young women typically have a lower MSNA compared to men [4,9,10], and sympathetic baroreflex sensitivity appears to vary during the menstrual cycle suggesting that the female reproductive hormones influence the neural control of the circulation. In this context, Christou et al. [11] demonstrated that the autonomic support of BP is lower in women than in men. The authors explained their findings by attributing the lower autonomic support of BP in women to the lower sympathetic nerve activity which has been previously observed. Additionally, it is possible that there are sex differences in the transduction of sympathetic nerve activity to vascular tone due to differences in the vascular α-adrenergic receptors. Several studies indicate that women have an attenuated vasoconstrictor response to α_1-adrenergic stimulation [12–15] but an enhanced vasodilator response to α_2-receptor stimulation [15,16]. Taken together, it appears that BP control in women is subject to distinct mechanisms of regulation compared to men. Thus, we aimed to investigate the differences in autonomic BP control. We specifically focused on the role of α-adrenergic receptors in the support of BP, and the importance of inter-individual variability within and between the sexes. We hypothesized that following blockade of the α-adrenergic receptors there would be a greater reduction in BP in the young men compared to the women.

Methods

Subjects

Thirty-one normotensive young adults (15 men) volunteered and gave their written informed consent before participating in the study (Table 1). Exclusion criteria were: age <18 or >35 years, tobacco use, acute/chronic disorders with alterations in cardiovascular function/structure, medications or contraindications to the drug phentolamine. Each female volunteer was studied in early follicular phase of the menstrual cycle/low hormone phase of contraceptive use [9,10]. The protocol was approved by the Institutional Review Board of the Mayo Clinic, and the study was performed in accordance with the Declaration of Helsinki.

Instrumentation and protocol

After an overnight fast, subjects in the supine position were instrumented with a brachial arterial catheter for the continuous measurement of blood pressure. HR was recorded with a 3-lead ECG. An 18-gauge peripheral forearm intravenous line was started to infuse phentolamine. Complete α-adrenergic blockade was induced using systemic doses of phentolamine administered as a 0.143 mg/kg intravenous bolus followed by a 0.0143 mg/kg continuous infusion [17]. For microneurography, a tungsten microelectrode was inserted in the peroneal nerve as described previously [4]. Baseline HR, BP, and MSNA were collected during 15 min of quiet supine rest and during 15 min of phentolamine infusion.

Data analysis

The BP, HR, and MSNA were averaged over the last 4 min of the rest period. During phentolamine infusion the HR, BP, and MSNA were averaged over 1 min after the nadir of the decrease in BP. The nadir in SBP, DBP, and MAP corresponded to ~70–85 heart beats after the start of the phentolamine infusion. MSNA was quantified as burst frequency (BF, bursts/min) or burst incidence (BI, bursts/100 hb) and analyzed by a single investigator, blinded to gender, as described previously [1,4].

Statistical analysis

Differences in the mean change in HR and BP after phentolamine between men and women were compared using an unpaired two-tailed *t* test. The relationship of changes in BP after phentolamine infusion to baseline MSNA and the change in MSNA during phentolamine

infusion was measured using Pearson's correlation coefficient. Estimation of α-adrenergic sensitivity was used to assess the amount of α-support on BP. Group average data are expressed as mean ± SEM; the alpha level was set at 0.05.

Results

Height, weight, body mass index, resting BP, and resting MSNA were lower in women compared to men, whereas resting HR was higher in women than in the men ($P < 0.05$; Table 1). Comparison of the maximal BP decrease during phentolamine displayed a significantly smaller decrease in systolic blood pressure (SBP) and mean arterial pressure (MAP) in women compared to men (ΔSBP −5 ± 2 vs. −12 ± 2 mmHg, $P = 0.03$; ΔMAP −9 ± 1 vs. −13 ± 1 mmHg, $P = 0.04$; Fig. 1). The change in diastolic blood pressure (DBP) immediately after phentolamine infusion was slightly lower in women than men (ΔDBP −9 ± 1 vs. −12 ± 1, $P = 0.07$), but the change in HR was not significantly different (ΔHR −13 ± 2 vs. −16 ± 2, $P = 0.22$). During the phentolamine infusion MSNA increased similarly in the women (ΔBF 14 ± 2 bursts/min; ΔBI 11 ± 2 bursts/100 hb) and men (ΔBF 15 ± 2 bursts/min; ΔBI 12 ± 2 bursts/100 hb, $P > 0.05$).

There was an inverse relationship between MSNA *before* phentolamine and the change in MAP during phentolamine infusion in women (BF $r = -0.67$, $P < 0.01$; Fig. 2 and BI r = −0.61, $P = 0.01$), conversely, this did not exist in the men (BF $r = -0.12$, $P = 0.6$; Fig. 2 and BI −0.10, $P = 0.7$). There was also an inverse relationship between the MSNA measured *during* phentolamine infusion and the change in MAP in women only (BF $r = -0.67$ and BI $r = -0.66$, $P < 0.01$). There was no relationship between the change in HR in response to phentolamine and baseline MSNA in women (BF $r = 0.39$, $P = 0.1$) or men (BF $r = 0.19$, $P = 0.4$).

Discussion

The main novel finding of the present study is that α-blockade with phentolamine induces a smaller reduction in BP in women than in men. This indicates that young women have a lower α-adrenergic support of BP compared to men of similar age. We also found a positive relationship between the resting level of MSNA and the phentolamine induced decrease in MAP in young women but not in young men. These findings support recent data from our lab that men and women rely on strikingly different integrated physiological mechanisms to maintain BP [8].

There are several possible explanations for our present findings. The group of young women had a lower level of resting MSNA compared to the young men. Consequently, blockade of the α-receptors had less of an effect on blood pressure in women compared to men. This coupled with the previously observed sex differences in α-adrenergic sensitivity [18] may contribute to the smaller reduction of BP to α-adrenergic blockade in women. However, it has been established that differences in α-adrenergic sensitivity may actually be a result of increased β_2-adrenergic receptor sensitivity in young women [15] as a result of the female sex hormones [16]. Thus, in women with high levels of MSNA, α-adrenergic vasoconstriction may be overwhelmed by β_2-adrenergic receptor-mediated vasodilation. In this context, we found that MSNA *before phentolamine* was inversely related to the reduction in MAP during phentolamine infusion in women. Additionally, we found that the level of MSNA measured *during* α-blockade was inversely related to the change in MAP, which indicated that women with a larger change in BP had a higher MSNA during phentolamine infusion. This suggests that with α-blockade, the β-adrenergic receptors caused un-opposed vasodilation. The relationship between the change in MAP and MSNA did not exist in the young men, which may be explained by altered α-receptor sensitivity

among individual men [4]. Men with a high MSNA have a lower α-adrenergic receptor responsiveness to norepinephrine [4]. Thus, blockade of the α-adrenergic receptors in men with a high MSNA may lead to a similar reduction in MAP as men who have a low level of MSNA.

The smaller reduction in MAP in the young women after α-adrenergic blockade may also be explained by sex differences in the relationship between MSNA and TPR [8]. Since MSNA is not related to the level of TPR among young women, the effect of α-blockade on the vasculature would have a lesser effect compared to young men. Conversely, in young men, TPR is positively related to MSNA [8]. Therefore, α-adrenergic blockade would have a greater effect on the vasculature and BP.

Limitations

Phentolamine is an unselective α-adrenergic antagonist; hence, the role of individual subtypes of α-receptors in BP support cannot be established; in future studies, testing/sampling of only one specific subtype will be necessary to evaluate the influence of α-receptor subtypes on sex-related α-receptor responsiveness. Another potential limitation is that the baroreflex was still intact. Therefore, changes in MAP may have been limited by differences in baroreflex responsiveness. However, HR and MSNA increased similarly in men and women suggesting that there were no differences in baroreflex activation and further imply that there were sex differences in vascular responsiveness.

Clinical relevance

Our data emphasize the importance of inter-individual differences in the regulation of arterial pressure. We found that after α-blockade in women, there was less of a decrease in BP compared to men which suggested that α-blockade was less effective in young women. However, when we focused on the inter-individual data we found that there was a positive relationship between MSNA and the reduction in arterial pressure after α-blockade in women. This suggests that α-adrenergic blockade may actually be effective in lowering BP in women with high sympathetic nerve activity. Conversely, in men this relationship was not observed, suggesting that α-blockade may be a less effective drug-based therapy in men with a high blood pressure that is associated with a hyper-adrenergic state. It should be considered, however, that all subjects in this study were healthy normotensive individuals.

Summary

We report that women have less α-adrenergic support of BP than men of similar age. In addition, women with a high MSNA during α-adrenergic blockade had a larger reduction in BP, which further suggests that men and women regulate blood pressure differently. These findings give important physiological insights into sex-related differences in integrative BP regulation mechanisms and highlight the importance of individualized medicine. Unraveling the complexity of BP regulation and its differences in gender may open new treatment options for BP disorders such as hypertension.

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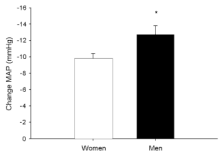

Fig. 1.

Comparison of the change in mean arterial pressure in men and women during phentolamine infusion. Mean ± SEM. **P* = 0.03

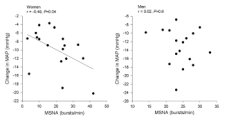

Fig. 2.

Relationship of baseline MSNA (BF) to changes in mean arterial blood pressure (MAP) in women (*left panel*, $n = 15$) and men (*right panel*, $n = 16$) during phentolamine infusion. Note that, in women, higher baseline MSNA was associated with a larger drop in MAP during phentolamine. The relationship was significant in the women ($P < 0.05$), but did not exist in the young men

Table 1

Subject characteristics during supine rest

Variable	Men (n = 15)	Women (n = 16)
Age (years)	25 ± 1	24 ± 1
Weight (kg)	79 ± 2	63 ± 2**
Height (cm)	180 ± 2	167 ± 1**
Body mass index (kg/m^2)	24 ± 1	23 ± 1**
Resting HR (beats/min)	59 ± 2	64 ± 2*
Baseline SBP (mmHg)	139 ± 3	126 ± 1**
Baseline DBP (mmHg)	75 ± 1	70 ± 1**
Baseline MAP (mmHg)	96 ± 2	90 ± 1**
Baseline MSNA (bursts/min)	24 ± 1	19 ± 2
Baseline MSNA (bursts/100 hb)	42 ± 3	32 ± 4*

Values are mean ± SEM

HR heart rate; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *MAP* mean arterial pressure; *MSNA* muscle sympathetic nerve activity; *BF* burst frequency; *BI* burst incidence

* $P < 0.05$,

** ** $P < 0.01$ versus men