Experimental Biology 1998 Symposium on Sex Steroids in Cardiovascular–Renal Physiology and Pathophysiology

GENDER DIFFERENCES IN SYMPATHETIC NERVOUS SYSTEM REGULATION

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SUMMARY

1. Females are protected against the development of hypertension. The purpose of the current review is to present the evidence for gender differences in the regulation of the sympatho-adrenal nervous system and to determine if these differences support the hypothesis that, in females, the regulation of the sympathetic nervous system (SNS) is altered such that sympatho-adrenal activation is attenuated or sympatho-adrenal inhibition is augmented.

2. The central control of sympatho-adrenal function is different in females and responses vary during the oestral and menstrual cycles. Pathways regulating the SNS appear to be less sensitive to excitatory stimuli and more sensitive to inhibitory stimuli in females compared with males.

3. Gender differences in arterial baroreflex sensitivity suggest that females may have a greater baroreflex sensitivity, such that alterations in blood pressure are more efficiently controlled than in males. Cardiopulmonary reflex inhibition of sympathetic nerve activity is greater in females, possibly resulting in a greater renal excretory function.

4. An attenuated sensitivity to adrenergic nerve stimulation, but not to noradrenaline (NA), suggests that gender differences in noradrenergic neurotransmission may protect females against sympathetic hyperactivity. Gender differences in the regulation of NA release via presynaptic α2-adrenoceptors, the vasoconstrictor response to the cotransmitter neuropeptide Y and the clearance of catecholamines are consistent with this hypothesis.

5. Similarly, attenuated stress-induced increases in plasma catecholamines in women suggest that females are less sensitive and/or less responsive to adrenal medullary activation. This is supported by findings of gender differences in adrenal medullary catecholamine content, release and degradation.

6. We conclude that there is strong evidence that supports the hypothesis that, in females, the regulation of the SNS is altered such that sympatho-adrenal activation is attenuated or sympatho-adrenal inhibition is augmented.

Key words: adrenal medulla, arterial baroreflex, blood pressure, cardiopulmonary reflex, catecholamines, gender, sympathetic nervous system.

INTRODUCTION

There is growing evidence for an influence of sex steroids on cardiovascular and renal physiology and pathophysiology. Epidemiological studies reveal that the prevalence of heart disease in premenopausal women is less than that in men of the same age.1 Similarly, the incidence and severity of hypertension, a major risk factor for heart disease, has been shown to be lower in women than men.2 Because these differences are not observed after the onset of menopause, it has been postulated that female sex hormones act to protect women from these cardiovascular diseases. Under resting conditions, healthy men and women have similar blood pressure (BP) but heart rate (HR) tends to be higher in women. Indices of sympathetic nervous system (SNS) activity suggest that normal resting function is similar in men and women3–6 or even reduced in women.7,8 These findings suggest that the SNS is regulated differently in males and females, which may ultimately contribute to gender differences in the development of hypertension.

Gender differences in hypertension have been clearly demonstrated in several experimental animal models, including Dahl salt-sensitive rats,9 deoxycorticosterone acetate/saline hypertension,10,11 spontaneously hypertensive rats12,13 and one-kidney renal wrap hypertension.14 In these models of hypertension in which ovariec-tomized females have been studied, removal of the ovaries augmented the hypertension. Although female sex hormones have been implicated in protecting females against hypertension, the mechanism by which this occurs is unknown. Because the SNS has been implicated in all these models of hypertension, it is possible that females are protected against hypertension because of a reduced activation of the SNS.

The purpose of the current review is to present evidence for gender differences in the regulation of the sympatho-adrenal nervous system and to determine if these differences support the hypothesis that, in females, the regulation of the SNS is altered such that sympatho-adrenal activation is attenuated or sympatho-adrenal inhibition is augmented. The approach will be to consider possible sites at which sympathetic regulation may differ in males and females. We will
focus on activation of central nervous system mechanisms, regulation of reflex-mediated control of peripheral sympathetic outflow and regulation of neurotransmitter release from peripheral sympathetic nerve terminals and the adrenal medulla.

CENTRAL REGULATION OF THE SNS

Central alterations in neural function have been demonstrated to contribute to hypertension. Consequently, the attenuated rise in BP in females may be associated with a reduced central activation of the SNS. Although little has been done to investigate gender differences in the regulation of central autonomic control, a few studies suggest that sex hormones may act centrally to alter sympathetic-adrenal function.

Unloading the baroreflex decreases afferent nerve activity to the nucleus tractus solitarius, which, in turn, decreases inhibition of the rostral ventrolateral medulla to stimulate the sympathetic-adrenal nervous system. Sinoaortic deafferentation mimics a baroreceptor unloading, leading to an acute sympathetic activation causing increased arterial pressure and HR. Preliminary data from this laboratory (JR Haywood, unpubl. obs., 1998) has demonstrated that when baroreceptor afferents are severed in females, a similar pattern of sympathetic activation occurs, resulting in the same rise in arterial pressure, HR and plasma noradrenaline (NA) over a 3 day period that was observed in males. The only difference is that plasma adrenaline does not rise in females.

Chemical or electrical stimulation of the paraventricular nucleus causes an activation of sympathetic-adrenal function with accompanying increases in arterial pressure and HR. We have observed that stimulation of N-methyl-D-aspartate (NMDA) glutamatergic receptors in males is characterized by an increase in arterial pressure, HR, plasma NA and adrenaline. In contrast, during di-oestrus or oestrus, females experience attenuated changes in BP and HR and no change in plasma adrenaline, yet the increase in plasma NA is similar to that in males. During pro-oestrus, females responded similarly to males.

Clonidine, an α2-adrenoceptor agonist, decreases SNS activity through central mechanisms. Male and female normotensive humans were given clonidine and found to respond with similar decreases in BP; however, these changes were associated with greater decreases in plasma NA in females than in males. In addition, adrenaline decreased only in women.

Together, these observations suggest that central control of sympathetic-adrenal function is different in females. In particular, pathways regulating the adrenal release of adrenaline appear to be less sensitive to excitatory stimuli and more sensitive to inhibitory stimuli compared with males. Furthermore, these responses may be related to the phase of the oestral and menstrual cycles.

BAROREFLEX REGULATION

Reflex changes in the SNS mediated via arterial and cardiopulmonary baroreceptors act to buffer changes in arterial pressure. Gender differences in baroreceptor reflex regulation of sympathetic nerve activity may provide a mechanism by which females are protected against the development of hypertension.

Arterial baroreflex

Baroreflex control of HR or nerve activity is typically represented as a sigmoidal relationship. The relationship between the changes in BP and the change in HR or nerve activity has a linear portion from which the sensitivity of the baroreflex can be calculated. The baroreflex curve also has two plateaus that correspond to the maximal activation and the maximal inhibition of HR or nerve activity during large decreases and increases in BP, respectively. Females may be protected from hypertension by altering the baroreflex in several ways: (i) an attenuated sympathetic nerve activation during baroreceptor unloading; (ii) a greater inhibition of the SNS during baroreceptor stimulation; or (iii) an increased ability to buffer changes in BP (i.e. a greater baroreflex sensitivity).

A commonly used index of arterial baroreceptor function is the baroreceptor reflex control of HR in response to bolus injections of vasopressor and vasodilator agents. Assuming that the changes in BP and HR are within the linear portion of the baroreflex curve, several studies using this approach have evaluated gender differences in baroreflex regulation of cardiac sympathetic nerve activity. The reflex bradycardia in response to increases in BP is diminished in women compared with men. This difference in reflex bradycardia has not been observed in male and female rats. A gender difference in reflex tachycardia in response to a decrease in BP has been observed in one study in which female rats responded with an attenuated increase in HR, but another study has found no gender differences in reflex-mediated tachycardia. In contrast, when bilateral carotid occlusion was used to unload arterial baroreceptors in rats, the resultant tachycardia was greater in females than in males. These studies do not generally support the hypothesis that females have a greater ability to attenuate sympathetic nerve activation or augment sympathetic nerve inhibition in the heart. However, it is important to note that baroreflex regulation of HR involves both the sympathetic and parasympathetic nervous systems and differences in parasympathetic nerve regulation may also contribute to gender differences in baroreflex control of HR.

In a recent study by Chen and DiCarlo, baroreflex regulation of HR and lumbar sympathetic nerve activity was evaluated in male and female rats. The gain of baroreflex control of HR as well as the maximum increase in HR was greater in females than in males. No gender differences were observed in baroreflex control of lumbar sympathetic nerve activity. Current studies in our laboratory assessing baroreflex control of renal sympathetic nerve activity using similar techniques suggest a somewhat different perspective. As a group, baroreflex control of renal nerve activity in females is comparable to males. However, when females are grouped according to the stage of the oestral cycle, females in pro-oestrus have a greater baroreflex gain and a greater maximal increase in nerve activity, while females in oestrus or di-oestrus have a reduced baroreflex gain and a decreased maximal increase in nerve activity compared with males (JR Haywood, unpubl. obs., 1998). These findings support the possibility that females may have a greater baroreflex gain, such that alterations in BP are more efficiently controlled than in males.

Cardiopulmonary baroreflex

Cardiopulmonary baroreceptors sense changes in central venous pressure that occur during shifts in venous volume usually associated with postural changes or changes in blood volume. A change in posture, such as from supine to standing, results in a decrease in central venous pressure, which triggers a reflex activation of the SNS. A study of gender differences in response to postural changes...
indicates that, when changing from sitting to standing positions, the resultant increases in HR and total peripheral resistance (TPR) were greater in women than men. When lower body negative pressure was used to simulate orthostatic-like stress, greater increases in HR were also observed in women, while the increase in TPR was either less than 24,31 or similar to that in men. 32 Cardiopulmonary baroreflex activation with head-up tilt caused similar increases in BP and HR in males and females; however, the associated increase in plasma NA was less in females. These studies of gender differences in cardiopulmonary reflex activation clearly demonstrate that gender differences exist; however, a consistent pattern in this difference remains to be clarified.

Cardiopulmonary receptors can also be activated by increases in blood volume leading to a reflex-mediated inhibition of sympathetic nerve activity. This reflex mechanism may be particularly important as a possible mechanism of protection against hypertension in females if the form of hypertension is initiated by retention of sodium and water. Under these circumstances, females may inhibit sympathetic nerve activity more efficiently, leading to a greater excretion of sodium and water than in males, thus delaying the onset of hypertension.

Direct measurements of lumbar sympathetic nerve activity during mechanical and chemical stimulation of cardiopulmonary receptors in male and female rats showed that females responded with greater decreases in nerve activity while there were no gender differences in BP and HR responses.33 Using 5% volume expansion with saline to activate cardiopulmonary receptors, we have observed (C Hinojosa-Laborde, unpubl. obs., 1998) that male and female rats respond with similar increases in right atrial pressure and similar decreases in renal sympathetic nerve activity (Fig. 1). Interestingly, female rats responded to the volume expansion with a greater increase in renal sodium excretion than males, indicating a gender difference in the responsiveness of the kidney to neurogenic regulation. The absence of a gender difference in renal sympathetic nerve response to volume expansion is most likely due to differences in the degree of cardiopulmonary receptor activation, which was substantially less than that observed in the study of lumbar sympathetic nerve activity.33 The hypothesis that females are protected against hypertension via an augmented sympathoinhibitory response is supported by the findings in lumbar sympathetic nerve activity and warrants further investigation.

**NORADRENERGIC NEUROTRANSMISSION**

**Peripheral sympathetic nerve terminals**

Gender differences in noradrenergic neurotransmission may provide a mechanism for protection of females against hypertension. Li and Duckles34 have shown that sensitivity to adrenergic nerve stimulation in rat tail arteries was greater in males compared with females, while there were no gender differences in sensitivity to NA. This difference in response to nerve stimulation was abolished by ovariectomy.35 There are various sites that can affect the amount of neurotransmitter available for eliciting an end-organ response (i.e. neurotransmitter synthesis, release and uptake).

Tyrosine hydroxylase is the rate-limiting enzyme in the synthesis of NA. Thus, changes in tyrosine hydroxylase activity have been used to assess catecholamine synthesis. However, no gender differences have been observed in tyrosine hydroxylase activity in vascular tissue.36 In addition, vascular tyrosine hydroxylase activity was not affected by gonadectomy or exogenous administration of female sex hormones.36

Sympathetic nerve stimulation in isolated hearts37 and tail arteries38 resulted in similar levels of released NA in male and female rats. When presynaptic α2-adrenoceptors were blocked, the enhanced release of NA to nerve stimulation was greater in isolated hearts from females compared with males.37 Ovariectomy was shown to abolish this augmented release of NA in females.37 These gender differences were not observed in the rat tail artery.38 Thus, female sex hormones may increase presynaptic α2-adrenoceptor activity, but this effect may be tissue specific. This increase in α2-adrenoceptor activity may be related to a greater number of α2-adrenoceptors in females than in males, an observation that has been made in platelets39 and the urethra.40

Release of cotransmitters may also contribute to gender differences in response to neurotransmission. Neuropeptide Y (NPY), which is localized and coreleased from sympathetic nerve terminals, has direct vasoconstrictor effects and can also potentiate NA-induced vasoconstriction.41 In areflexic pithed rats, the vasoconstrictor effects of NPY are greater in males than in females.42 In contrast, the degree of NPY-potentiated contraction elicited by adrenergic nerve stimulation was greater in rat tail arteries from females than males.43

Gender differences in response to adrenergic nerve stimulation may be a result of differences in the clearance of released NA (i.e. neuronal and extraneuronal uptake). Unfortunately, this area has not...
been extensively studied. An increase in adrenaline clearance in women is suggested by a study that compared the effects of exogenous adrenaline in men and women. It was observed that similar doses of adrenaline resulted in greater increases in plasma levels of adrenaline in men compared with women. However, the direct assessment of the contribution of neuronal and extraneuronal uptake to the release of NA during nerve stimulation in cardiovascular tissue has not been investigated. Considering the evidence that exogenous oestrogen can attenuate both neuronal and extraneuronal uptake of catecholamines in various tissues, more studies are needed to define gender differences in catecholamine inactivation.

Adrenal medulla

Cardiovascular responses to stress are generally gender dependent. Men typically respond to stress with greater increases in BP, HR and plasma levels of catecholamines than women. As described earlier, experiments studying central sympatho-adrenal control indicated less adrenal activation in females. These findings strongly suggest that there are gender differences in the sympathetic activation of the adrenal medulla, which results in attenuated responses in females. Animal studies support this possibility. The adrenal medullary content of NA and adrenaline in female rats varies with the oestral cycle and is less than that in male rats. Similarly, oestradiol treatment has been shown to decrease adrenal medullary NA content in female rats and also decrease the basal release of catecholamines from rat and bovine adrenal glands. These decreases in content and release do not appear to be related to decreases in catecholamine synthesis because oestrogen treatment has been shown to increase adrenal tyrosine hydroxylase activity in female rats. Finally, the degradation of adrenal catecholamines is also affected by sex hormones. The levels of monoamine oxidase and catechol-O-methyl transferase activity vary during the oestral cycle and ovariectomy causes a reduction in the activity of these enzymes. Administration of oestrogen to ovariectomized rats results in an increase in adrenal medullary catechol-O-methyl transferase activity, thus reversing the effect of ovariectomy.

CONCLUSIONS

Clear evidence exists for differences in the regulation of the sympatho-adrenal nervous system between males and females. At each level of neural control examined in the present review, females were able to limit the activation or enhance the inhibition of the SNS more effectively than males during at least part of the oestral/menstrual cycle. These observations suggest that the ability of females to more tightly control the SNS and, subsequently, arterial pressure may serve as a mechanism whereby sex hormones protect women against hypertension.

ACKNOWLEDGEMENTS

The authors thank Ms Francis Nieves-Roldan for her expert technical support. This work was supported by awards from the National Institutes of Health (HL 30650 and HL56752 to JRH) and (HL03153 to CHL) and the American Heart Association (94008450 to CHL).

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