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REVIEW

Autonomic control of body temperature and blood pressure: influences of female sex hormones

Nisha Charkoudian[1] · Emma C. J. Hart[2] · Jill N. Barnes[3] · Michael J. Joyner[4]

Abstract Female reproductive hormones exert important non-reproductive influences on autonomic regulation of body temperature and blood pressure. Estradiol and progesterone influence thermoregulation both centrally and peripherally, where estradiol tends to promote heat dissipation, and progesterone tends to promote heat conservation and higher body temperatures. Changes in thermoregulation over the course of the menstrual cycle and with hot flashes at menopause are mediated by hormonal influences on neural control of skin blood flow and sweating. The influence of estradiol is to promote vasodilation, which, in the skin, results in greater heat dissipation. In the context of blood pressure regulation, both central and peripheral hormonal influences are important as well. Peripherally, the vasodilator influence of estradiol contributes to the lower blood pressures and smaller risk of hypertension seen in young women compared to young men. This is in part due to a mechanism by which estradiol augments beta-adrenergic receptor mediated vasodilation, offsetting alpha-adrenergic vasoconstriction, and resulting in a weak relationship between muscle sympathetic nerve activity and total peripheral resistance, and between muscle sympathetic nerve activity and blood pressure. After menopause, with the loss of reproductive hormones, sympathetic nerve activity, peripheral resistance and blood pressure become more strongly related, and sympathetic nerve activity (which increases with age) becomes a more important contributor to the prevailing level of blood pressure. Continuing to increase our understanding of sex hormone influences on body temperature and blood pressure regulation will provide important insight for optimization of individualized health care for future generations of women.

Keywords Thermoregulation · Sympathetic nerve activity · Women · Sex differences · Aging

Introduction

Female reproductive hormones exert important non-reproductive influences on integrative physiology. These influences change over the lifespan as a function of short and long-term changes in hormone levels. In human autonomic physiology, these include important effects on the regulation of body temperature and blood pressure. The goal of this brief review is to summarize the influences of female sex hormones on autonomic mechanisms of thermoregulation and blood pressure regulation across the lifespan.

Autonomic mechanisms of thermoregulation

Thermoregulation in humans is controlled centrally by hypothalamic nuclei, which elicit reflex adjustments to maintain body temperature at or near 37 °C, despite a wide range of environments (exogenous heat loads) and activity levels (endogenous heat loads). The primary central neural control of thermoregulation in mammals is the preoptic area of the anterior hypothalamus (PO/AH). Increases in

✉ Nisha Charkoudian
nisha.charkoudian.civ@mail.mil

1 U.S. Army Research Institute of Environmental Medicine, 15 General Greene Avenue, Natick, MA 01760, USA

2 University of Bristol, Bristol, UK

3 University of Wisconsin-Madison, Madison, WI, USA

4 Department of Anesthesiology, Mayo Clinic, Rochester, MN, USA

body core and/or surface temperature are sensed by the PO/AH, which elicits increases in heat dissipation responses [3, 4]. In general, integrated thermoregulatory responses are thought to respond in a proportional manner such that the input of core and surface temperatures are approximately 90 and 10%, respectively [45]. However, the specifics of this proportionality are not constant, and are altered by factors including activity, core-to-skin thermal gradients, and rate of change of skin temperature, among others [37, 45].

In response to increased body temperature in humans, reflex increases in cutaneous vasodilation and sweating increase heat dissipation, minimizing increases in body temperature during heat exposure or exercise [7, 8]. Conversely, decreases in body temperature result in decreases in heat dissipation (via cutaneous vasoconstriction) and increases in heat generation (via shivering).

Temperature sensitive neurons in the PO/AH respond to their own local temperature by increasing or decreasing their firing rates. Warm-sensitive neurons, for example, increase firing when their temperature increases. Increased firing of these neurons ultimately leads to increases in systemic heat dissipation responses, whereas combinations of cold-sensitive and temperature-insensitive neuronal firing result in decreases in heat dissipation and increased heat generation [3, 4].

The human skin circulation is one of the major effectors of heat dissipation. Human skin blood flow is controlled by two branches of the sympathetic nervous system. Sympathetic vasoconstrictor nerves are noradrenergic, releasing norepinephrine and co-transmitters and are responsible for minor variations in skin blood flow that occur during most daily activities. The sympathetic active vasodilator system works via cholinergic nerve co-transmission, the mechanisms for which are incompletely understood [7]. The active vasodilator system is not tonically active, and is activated only during increases in core body temperature such as during heat exposure or exercise. These nerves are responsible for approximately 80–90% of the very large increases in skin blood flow that are seen with core hyperthermia. Local heating of the skin causes extensive vasodilation. This local response is largely dependent on nitric oxide, and does not rely on reflex sympathetic innervation [41, 42]. Prolonged local warming to 41–44 °C can result in maximal vasodilation in the skin microcirculation [31, 36]. Local cooling causes a localized vasoconstriction [25], which involves local neurotransmitter release from sympathetic nerve endings, but does not require intact reflex innervation [42]. Thus the local influences of temperature can complement the reflex influences of environment or exercise with regard to heat dissipation or heat conservation. Sweating works in conjunction with skin blood flow to increase dissipation of heat

to the environment. Sweating is mediated by sympathetic cholinergic nerves which are also activated during increases in core temperature, although not always with the same time course as active vasodilation in the skin. For more in-depth review of mechanisms of thermoregulation, see [3, 7, 29].

Thermoregulatory influences of estradiol and progesterone

In addition to subserving thermoregulatory reflexes, the control of skin blood flow and sweating are modified by numerous non-thermal influences [7, 13]. Among these are circulating estradiol and progesterone. In general, estradiol appears to promote vasodilation, heat dissipation and lower body temperatures, whereas progesterone seems to promote less vasodilation, heat conservation, and higher body temperatures. Although not all of the mechanisms for these effects have been elucidated, several lines of evidence are supportive of both central and peripheral influences of the hormones. As noted above, hypothalamic warm-sensitive neurons are responsible for initiating heat dissipation responses. Silva and Boulant demonstrated that these neurons increase their activity (in rat brain slice preparations) in response to addition of estradiol to their local environment [46].

At the systemic level, Stephenson and Kolka demonstrated that sweating responses were initiated at lower core body temperatures when endogenous estradiol was elevated unopposed by progesterone (late follicular/pre-ovulatory phase of the menstrual cycle) [49]. Interestingly, when estradiol and progesterone are elevated concurrently, such as in the mid-luteal phase of the menstrual cycle or with the exogenous hormones in oral contraceptives, the influence of progesterone appears to dominate. Thus, in the mid-luteal phase of the menstrual cycle, the core temperature threshold to initiate sweating and cutaneous vasodilation is shifted to higher core temperatures [9, 50]. This shift in thermoregulatory control also occurs with the exogenous hormones in oral contraceptives [9, 10]. Interestingly, the higher body temperature and thermoregulatory shift are not inhibited by ibuprofen (cyclooxygenase inhibitor), suggesting a mechanism different from that seen with an infection-induced fever [9].

Thermoregulation and pregnancy

Although not as well studied, the thermoregulatory influences of estradiol and progesterone are also observed during normal pregnancy [21]. Body temperature increases by a few tenths of a degree during the first trimester, and

then falls throughout the second and third trimesters to approximately baseline levels, as measured 1 year after pregnancy [21]. These changes are consistent with hormonal fluctuations, with relatively large increases in progesterone + estradiol during the first trimester and higher estradiol (with relatively low progesterone) during the second and third trimesters.

Thermoregulation and aging

Thermoregulatory responses to both increases and decreases in body temperature are impaired with healthy aging [15, 32], and may be further impaired with various age-related diseases including diabetes and hypertension [26, 27, 48]. The mechanisms for these changes include changes in reflex neural as well as local vascular and sweat gland mechanisms [15]. These result in overall lower heat dissipation responses (skin blood flow and sweating) in older compared to younger healthy people, as well as decreased cutaneous vasoconstrictor responses to body cooling [15]. Interestingly, increasing physical activity and fitness can partially reverse the age-related decrements in heat dissipation responses [24].

The thermoregulatory influences of the sex hormones in young women are relatively subtle. They usually cannot be "sensed" (i.e., a woman usually does not feel warmer or cooler at different times in her cycle), and do not result in impairments in overall ability to regulate body temperature [13] or in any symptoms or decreased quality of life. In contrast, changes in thermoregulation in older women, particularly during the menopausal transition, can be quite striking and have a marked influence on thermal comfort and overall quality of life. Hot flashes remain poorly understood, but recent work points to some of the mechanisms. Hot flashes (or flushes) involve sudden, transient, increases in sensation of warmth, accompanied by cutaneous vasodilation and sweating, often associated with sensations of dizziness or other discomfort. The sensation of warmth most likely comes from the increased blood flow (convective heat transfer) to the skin, not from an actual increase in core body temperature. Recent work from Low and colleagues identified that the large increases in skin blood flow seen during a hot flash can be blocked with local administration of botulinum toxin [35]. Since botulinum toxin works by blocking cholinergic neurotransmission, it effectively blocks the active vasodilator arm of the neural control of skin blood flow. The data therefore suggest that the large increases in skin blood flow are mediated by sympathetic neurogenic mechanisms (i.e., the active vasodilator system). Consistent with this idea were findings that directly measured skin sympathetic

nerve activity (SSNA) increasing ∼4-fold during hot flashes [35].

Interestingly, blood pressure did not consistently change during hot flashes. In a separate study, Low and colleagues found that blood pressure was decreased during a hot flash in only 5 of the 12 women studied [34]. Skin blood flow and heart rate responses were not different between these five women and the seven women in whom blood pressure did not decrease. The exact mechanism(s) causing reductions in blood pressure during hot flashes in a subset of women is currently unclear.

Interactions of thermo- and baro-regulation in humans

Because of the striking redistribution of blood flow that can occur with human thermoregulatory responses (most notably the movement of large volumes of blood to, or away from, the skin circulation), autonomic regulation of body temperature and of blood pressure often work together in an integrated fashion. High demand for skin blood flow (e.g., due to a hot environment) may impair the ability of the system to maintain arterial blood pressure during orthostasis, particularly during prolonged heat exposure [44]. Conversely, cooling the skin and causing cutaneous vasoconstriction can improve orthostatic tolerance [14]. As noted above, changes in body temperature and blood pressure that can accompany hot flashes are a particularly striking example of the intersection of body temperature and blood pressure regulation [34].

Thus thermoregulation may impact the control of arterial blood pressure, which requires a balance of sympathetic control of peripheral vasoconstriction with neural and non-neural factors controlling cardiac output and vascular resistance. The "neural-hemodynamic balance hypothesis" refers to a collection of observations regarding relationships among vascular sympathetic nerve activity, arterial blood pressure, cardiac output and peripheral blood flow [11, 12, 18]. From the earliest direct measurements of muscle sympathetic nerve activity (MSNA) in humans, it has been recognized that there is a striking inter-individual variability in resting MSNA. MSNA can vary five- to tenfold among otherwise similar, healthy and normotensive humans [19, 47, 52]. Even more striking, this large variability is not associated with variability in arterial blood pressure. This lack of association, among healthy young men, is due in part to a balance between cardiac output (CO) and MSNA—individuals with higher MSNA (and higher total peripheral resistance [TPR]) have lower CO, and vice versa [11]. Age-related increases in resting MSNA were also shown to be inversely proportional to blood volume in men (but not women) [2]. Other factors, such as

lower vascular adrenergic responsiveness in people with higher MSNA, also contribute to this integrated balance in the normal regulation of blood pressure [12].

Influences of estradiol on blood pressure regulation

The hemodynamic influences of female reproductive hormones result in striking differences between men and women in sympathetic regulation of blood pressure. Among young, healthy people, women tend to have lower sympathetic neural activity and lower blood pressure compared to men of similar age. Women seem to operate (in general) on the lower end of the blood pressure "spectrum"—young women have lower risk of hypertension than young men, and have greater incidence of so-called "hypotensive" disorders, including orthostatic intolerance and/or hypotension [43]. This is apparently due to a protective effect of estradiol, which is lost at menopause, at which point both sympathetic nerve activity and blood pressure show a sharp increase [1, 38].

In general, the inter-individual variability in MSNA, and the lack of relationship between MSNA and blood pressure, are similar in women and in men [16, 17]. In one larger cohort study, we found that this conclusion may vary slightly depending on whether women are taking oral contraceptives (OC) [23]. Young women with natural menstrual cycles (not taking OC) showed a statistically significant relationship between MSNA and mean arterial pressure ($r = 0.27$, $P = 0.02$) [23]. Even in this case, however, the relationship was minimal: women with MSNA that was several-fold higher had arterial pressure values that were only a few mmHg higher than those with lower MSNA [23].

We evaluated the relationships among CO, MSNA and TPR in young women to assess whether the "balancing" factors were similar to those seen in young men [17]. We were surprised to note that there was no relationship between MSNA and CO or TPR among young women. This was true even when larger groups of data were analyzed together [23]. Therefore, there must be some other variable that "balances out" the effect of greater vasoconstrictor nerve activity on the prevailing level of arterial pressure. In an earlier study from Kneale and colleagues [33], brachial arterial infusions of norepinephrine caused progressive dose-dependent vasoconstriction in young men, but caused minimal vasoconstriction in young women. When the investigators administered propranolol (beta-adrenergic blockade), the norepinephrine caused similar vasoconstriction to that seen in the men. This suggests that, in young women, beta-adrenergic vasodilation minimizes some of the vasoconstrictor influence of

sympathetic noradrenergic nerve activity. We tested whether this was true on a systemic basis by evaluating the relationship between MSNA and TPR in young men and women before and during systemic propranolol administration [17]. Before propranolol, young men showed the direct MSNA–TPR relationship, and young women did not show a significant relationship between MSNA and TPR. During beta blockade, this relationship became significant and positive in young women, and remained significant and positive in young men. These data suggest that beta-adrenergic vasodilation offsets alpha-adrenergic vasoconstriction in young healthy women, and is consistent with the nitric oxide-promoting influences of estradiol that are seen in other contexts [51]. These represent a different set of mechanisms by which MSNA and arterial pressure are unrelated in this group.

Sympathetic nerve activity in pregnancy

Blood pressure regulation during pregnancy varies widely, and blood pressure levels can decrease, increase or stay the same depending on various combinations of interactions among blood volume, sympathetic nerve activity, vascular stiffness, and other variables. Although a detailed overview of blood pressure regulation during pregnancy is outside the scope of the present paper, a few recent reports have provided novel insight into changes in sympathetic neural mechanisms that are relevant to the present discussion.

Sympathetic nerve activity increases during normotensive pregnancy. Recent work from Jarvis and colleagues indicates that MSNA increases as early as 6 weeks gestation [28]. The increase in MSNA appears to persist throughout pregnancy, and can become quite marked in some women [53, 54]. During healthy pregnancy, this significant sympathoexcitation is not associated with any increase in arterial pressure. This appears to be due to a combination of blunted sympathetic neurovascular transduction during pregnancy [28] and altered baroreflex control of heart rate and sympathetic nerve activity [53]. Importantly, the sympathoexcitation associated with pregnancy appears to differ between Caucasian and Asian women. Asian women have smaller increases in sympathetic nerve activity with pregnancy, both during supine rest and head-up tilt [39]. This likely contributes to the lower blood pressure in Asian women before and during pregnancy, and lower incidence of pregnancy-related hypertensive disorders [39]. Continued progress in this area will provide important information regarding differences between healthy cardiovascular regulation during pregnancy and common disorders including hypertension and pre-eclampsia.
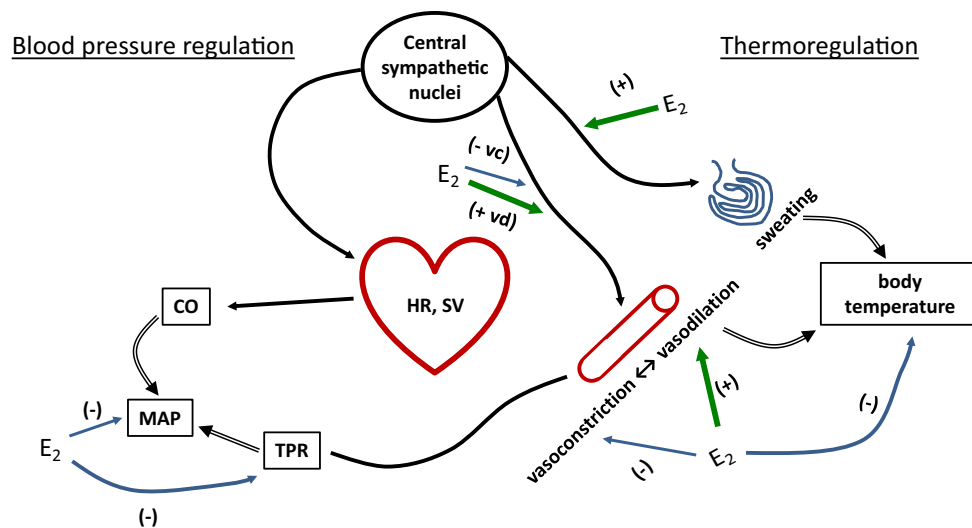
Fig. 1 Influences of female reproductive hormones (primarily estradiol, [E$_2$]) on the systems that regulate blood pressure and body temperature. These systems work together in an integrated balance, coordinated by the autonomic nervous system. One of the major effects of E$_2$ is to limit vasoconstriction (vc) and promote vasodilation (vd), which decreases blood pressure (via decreased TPR) and body temperature (via increased heat dissipation). This figure does not include the influences of progesterone (which are less well understood), or of hormones during pregnancy. *MAP* mean arterial pressure, *CO* cardiac output, *HR* heart rate, *SV* stroke volume, *TPR* total peripheral resistance

Neural-hemodynamic balance and aging

Sympathetic nerve activity increases consistently with increasing age; this likely contributes importantly to the increase in blood pressure and risk of hypertension in older age groups. Interestingly, the lack of relationship among individuals between MSNA and blood pressure becomes a significant, positive relationship in groups of people over 40 years of age [38]. Thus, individuals with higher MSNA tend to have higher blood pressure in older groups, even among normotensive people. This suggests that the balances among cardiac output, sympathetic nerve activity and vasodilation/vasoconstriction that exist in younger people do not exist, or are minimized, in older groups.

Another important implication of these observations is that vascular sympathetic nerve activity, itself, becomes a more important determinant of arterial blood pressure as people age. This latter idea has received direct support from ganglionic blockade studies. Autonomic ganglia can be pharmacologically blocked, and the resultant drop in blood pressure is considered to represent the extent to which the autonomic nervous system was "supporting" blood pressure at baseline. A variety of drugs are used in animal models (e.g., hexamethonium); in humans, the most common is trimethaphan. Jones and colleagues [30] found that ganglionic blockade via intravenous trimethaphan resulted in larger drops in blood pressure in a group of older men compared to a group of younger men. Furthermore, the extent of drop in blood pressure was proportional

to the original (pre-blockade) level of sympathetic nerve activity across all subjects.

Recently, Barnes and colleagues evaluated whether autonomic support of blood pressure was similarly changed with age in women [1]. We measured MSNA, blood pressure and cardiac output before and during ganglionic blockade with trimethaphan and found, as in men, that blood pressure drops were greater in a group of older women (average age ∼62 years) compared to a group of younger women (average age ∼24 years). Older women had on average higher MSNA at baseline, and individual drops in blood pressure were strongly correlated with baseline levels of MSNA [1]. In a separate report, we evaluated the blood pressure "setpoint" or midpoint of the baroreflex curve (T50) in premenopausal women and postmenopausal women. Postmenopausal women had an approximately 8 mmHg higher T50 compared with premenopausal women, suggesting that female hormones influence baroreflex control of blood pressure [40]. Together, these data suggest a major role for vascular sympathetic nerve activity in determining baseline blood pressure in the older women. In the same study, we evaluated whether beta-adrenergic vasodilation was a major factor in the relationship between MSNA and TPR (as it was in young women). In the older group, there was a significant positive relationship between MSNA and TPR both before and during beta-blockade, suggesting that post-menopausal women do not have the "offsetting" effect of beta-adrenergic vasodilation seen in younger women [1]. This also supports the idea that estradiol (or some combination of

female sex hormones) is responsible for the augmented beta adrenergic vasodilation seen in younger women.

In older men and women, the relationship between MSNA and MAP is positive, because they appear to lose the "balancing" factors that are seen in younger men and women. In older women, this appears to be due to the loss of beta-adrenergic vasodilation which offsets the pressor effects of SNA in younger women. In older men, this appears to be due to a loss of the balance between MSNA and cardiac output. The mechanisms behind this are not clear, but may be related to increases in circulating and/or local vasoconstrictors (e.g., endothelin) in older men [20]. Vascular stiffness may also contribute [5, 6, 22]. The net result of these changes is that sympathetic vasoconstrictor nerve activity, which is increasing with age, becomes a more important contributor to the prevailing blood pressure level in both men and women, and the effect in women is particularly striking when circulating hormone levels change during the menopausal years.

In summary, the influences of female sex hormones on autonomic control include important effects on both body temperature regulation and blood pressure regulation in humans. There is some evidence that these influences may overlap (for example, the changes in thermoregulation that occur with hot flashes are associated with decreases in blood pressure in some women). These influences and their potential for overlap are summarized in Fig. 1. Better understanding of these potential interactive influences is an important goal for future research, particularly as it might relate to treatment of thermal symptom development with menopause and/or blood pressure changes in older women.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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