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Review

Sex hormone effects on autonomic mechanisms of thermoregulation in humans

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ABSTRACT

Autonomic mechanisms are fundamental to human physiological thermoregulation, and female reproductive hormones have substantial influences on several aspects of these mechanisms. Of these, the best recognized are the thermoregulatory responses that occur at menopause (hot flushes) and the changes in body temperature within the menstrual cycle which may help couples predict ovulation. Our goal in this brief review is to summarize current knowledge regarding the influences of reproductive hormones on autonomic mechanisms in human thermoregulation. In general, estrogens tend to promote lower body temperatures via augmentation of heat dissipation responses, whereas progesterone tends to promote higher body temperatures. Recent evidence suggests specific influences of estrogens on central autonomic nuclei involved in control of skin blood flow and sweating. Estrogens also augment vasodilation by direct effects on peripheral blood vessels. Influences of progesterone are less well understood, but include both centrally regulated changes in thermoregulatory set-point as well as and peripheral effects, including augmented vasoconstriction in the skin. We conclude with a brief discussion of thermoregulatory adjustments associated with changing hormone levels during menopause, pregnancy and polycystic ovary syndrome.

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Contents

1. Introduction

Human physiological thermoregulation keeps body temperature constant over a wide range of environments and activity levels. Our ability to thermoregulate so effectively is due to a complex interplay of systems which are fundamentally dependent upon autonomic mechanisms. In neutral to cool environments, changes in skin blood flow are the primary means by which we maintain body temperature. These changes are controlled by sympathetic noradrenergic nerves of the cutaneous vasoconstrictor system, which are responsible for keeping body temperature constant during most daily activities (Charkoudian, 2010). Sympathetic nerves also innervate brown adipose tissue, a source of non-shivering thermogenesis during exposure to cold (Morrison and Madden, 2014). Moreover, during cold exposure,

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autonomic homeostatic responses (thermogenesis and vasoconstriction) to restore body temperature increase energy expenditure through both shivering and nonshivering thermogenesis, and increase peripheral insulation via decreased skin blood flow (Charkoudian, 2010; Johnson et al., 2011; Lowell and Spiegelman, 2000).

During heat exposure and exercise, core body temperature increases, and sympathetic cholinergic nerves elicit sweating from eccrine sweat glands, the evaporation of which represents a major avenue of heat dissipation during hyperthermia in humans (Gagnon and Kenny, 2012a). Large increases in skin blood flow, which increase convective heat transfer to the surface of the body, are mediated by the sympathetic active vasodilator system. This occurs via cholinergic co-transmission, and includes several mediators such as vasoactive intestinal peptide (VIP), nitric oxide (NO) and prostaglandins, among others (Charkoudian, 2010). The vasodilator system is not tonically active, but once activated during core hyperthermia, is responsible for 80–90% of the large increases in skin blood flow that occur with heat stress (Charkoudian, 2010; Rowell, 1983). Furthermore, both sympathetic and parasympathetic mechanisms contribute to changes in heart rate (Gorman and Proppe, 1984), which are major contributors to corresponding changes in cardiac output needed to support circulatory responses to thermal stress (Johnson and Proppe, 1996).

Thus, autonomic mechanisms are central to thermoregulation in humans and other mammals. In the present brief review, our goals are to provide an overview of current understanding concerning the influences of female reproductive hormones on the autonomic mechanisms involved in integrative physiological thermoregulation, and to point out areas in which information is incomplete, representing important avenues for future work.

In some contexts, the relevance of female reproductive hormone effects on thermoregulation is well-recognized — for example, hot flushes (or vasomotor symptoms, VMS) are a classic symptom of menopause, including cutaneous vasodilation and sweating. This phenomenon substantially reduces quality of life in about 80% of women going through menopause (Kelly and Ronnekleiv, 2015). The fact that estrogen replacement therapy tends to decrease the occurrence of these events points to an important thermoregulatory influence of this hormone.

In other contexts, the influences of female hormones are more subtle. In young women, basal body temperature fluctuates by about 0.5–0.8 °C over the course of the normal menstrual cycle, decreasing slightly just prior to ovulation when estrogen exposure is elevated unopposed by progesterone, and increasing during the mid-luteal phase when both progesterone and estrogens are elevated (Charkoudian and Johnson, 1999a; Stephenson and Kolka, 1999, 1985). The control of thermoregulation is similarly shifted in each phase of the cycle, suggesting that these are regulated changes in body temperature and not simply coincidental effects of changes in resting metabolism or skin blood flow (Charkoudian and Johnson, 2000). The evolutionary or adaptive "reason" for such changes in body temperature over the course of the menstrual cycle has been debated; one possibility is that the mid-luteal increase in temperature might facilitate embryonic implantation, if fertilization were to occur in a given cycle (Charkoudian and Johnson, 2000).

2. Influence of female reproductive hormones

2.1. Central control of thermoregulation

The primary central area responsible for control of body temperature is the preoptic region of the anterior hypothalamus (PO/AH). Additionally, the median preoptic nucleus, medullary raphé region and dorsomedial hypothalamus have been identified as important areas for integration of thermoregulatory signals with cardiovascular and other related physiological systems (McAllen et al., 2006; McKinley et al., 2015; Nakamura, 2011). In the PO/AH region, various sub-populations of neurons have been identified which correspond to distinct physiological responses (Boulant, 2006). Warm-sensitive neurons increase their firing rate in response to increases in temperature, and are responsible for eliciting physiological heat dissipation responses including sweating and cutaneous vasodilation. Cold-sensitive neurons and temperature-insensitive neurons are involved in responses to body cooling that include cutaneous vasoconstriction and shivering.

Estrogen receptors have been localized in several of the hypothalamic structures involved in temperature regulation (Rance et al., 2013). Silva and Boulant demonstrated that exposure to estrogen (rat brain slice preparations) caused an increase in firing rate of warm-sensitive neurons (Silva and Boulant, 1986). This is consistent with observations in intact humans that increases in circulating estrogens appear to augment heat dissipation responses, including cutaneous vasodilation and sweating (Stephenson and Kolka, 1999). The specific influences of progesterone on central neurons controlling body temperature are less clear.

Estrogen signaling in the hypothalamus appears to be mediated via both nuclear ("classical" steroid receptor mechanism) and membrane receptor pathways via the estrogen receptors ER-alpha and ER-beta (Kelly and Ronnekleiv, 2015). With regard to central effects of estrogen, a specific sub-population of neurons within the arcuate nucleus of the rat (which is the homolog of the infundibular nucleus in humans) has been shown to be involved in the thermoregulatory effects of estrogen (Mittelman-Smith et al., 2012; Rance et al., 2013). These neurons, called KNDy because they express kisspeptin, neurokinin B, neurokinin-3 receptor and dynorphin, also express ER-alpha. Withdrawal of estrogen caused changes in the morphology of these neurons, and in their interaction with nuclei involved in thermoregulation, including the median preoptic nucleus (Mittelman-Smith et al., 2012). It has been proposed that changes in these neurons may be involved in the altered thermoregulation (eg, hot flushes) associated with changing estrogen levels during the perimenopausal and menopausal years (Rance et al., 2013).

2.2. Integrated physiological thermoregulatory responses

In terms of integrated thermoregulatory responses, the central effects of female reproductive hormones manifest themselves as changes in the threshold temperature which triggers the onset of thermoregulatory heat dissipation responses, cutaneous vasodilation and sweating. These changes are summarized in Fig. 2. The mechanism for increased temperature during the luteal phase of the menstrual cycle is generally thought to be associated with a progesterone-related shift to a higher thermoregulatory set-point, suggesting the thermoregulatory actions of these sex hormones take place at the thermosensitive neurons in the CNS. Indeed, unopposed progestins administered via hormonal contraceptive pills increased the regulated body temperature, as both core temperature and the core temperature threshold for sweating increased during exercise. Moreover, estrogen administered with progestin reversed these thermoregulatory changes (Stachenfeld et al., 2000). Similarly, in post-menopausal women, the administration of exogenous hormone replacement therapy containing only estrogens was associated with a lower body temperature and a lower threshold for the onset of cutaneous vasodilation and sweating during body heating (Brooks et al., 1997). Addition of progestin to the HRT resulted in a reversal of these effects (Brooks et al., 1997).

During the luteal phase of the menstrual cycle, the core temperature at which cutaneous vasodilator and sweating responses are initiated is about 0.5 °C higher compared to the early follicular phase (Charkoudian and Johnson, 1999a; Stephenson and Kolka, 1985) (see Fig. 1). This shift in thermoregulatory control is also seen when sweating and skin blood flow responses are compared between the hormone pill and placebo phases of oral contraceptive use (Charkoudian and Johnson, 1999a, 1997). Interestingly, although the shifts in body temperature and thermoregulatory control are qualitatively similar to an infection-induced fever, these shifts are not prostaglandin-dependent, and thus not mechanistically similar to a classical fever (Charkoudian and Johnson, 1999a). The shifts

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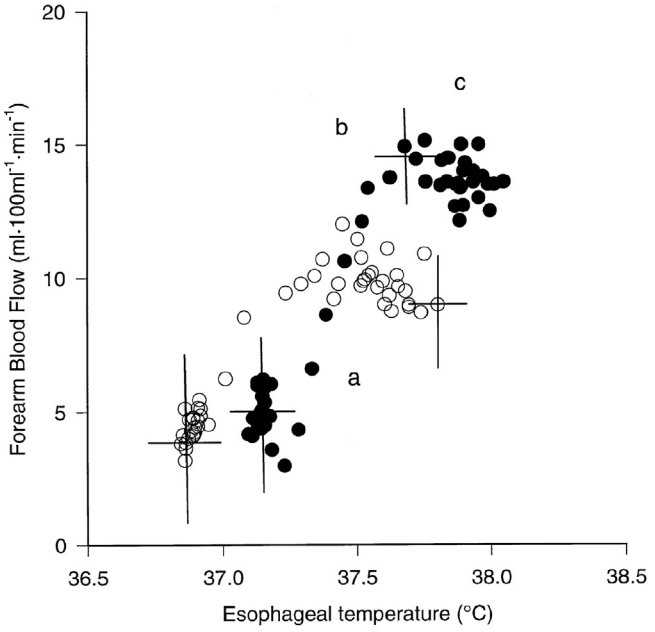

Fig. 1. Forearm blood flow responses (representing skin blood flow increases) as a function of core body (esophageal) temperature during prolonged exercise in the heat in the early follicular (open symbols) and mid-luteal (closed symbols) phases. Note the increased threshold temperature for the onset of the response in the luteal phase (likely a central effect), as well as the increased steady-state vasodilation (likely a peripheral influence of estradiol). Reproduced with permission from (Kolka and Stephenson, 1997).

in heat dissipation responses result in a decrease in heat dissipation for any given level of core temperature during heat exposure or exercise, and the maintenance of a higher core temperature relative to the same condition in the early follicular phase.

The sensitivity, or responsiveness, of the sweating or skin blood flow response refers to the increment in the response for a given increment in body temperature. Sensitivity can be represented by the slope of the relationship between sweating/skin blood flow and core temperature (Charkoudian, 2003). Thus, a person with higher sensitivity would be more responsive to a given increase in body temperature. Although one study showed a higher sensitivity of sweating as a function of mean body temperature in the luteal phase (Hessemer and Bruck, 1985), there does not appear to be a consistent influence of reproductive hormones on the sensitivity of skin blood flow or sweating responses (when expressed as a function of core body temperature) during exercise or passive body heating (Charkoudian and Johnson, 1999a, 1997; Stephenson and Kolka, 1985).

Integrated physiological responses to body cooling also appear to be shifted to higher regulated body temperatures when progesterone + estrogen are elevated. The cutaneous vasoconstrictor response to a ramp whole body cooling protocol (using water-perfused suits) was shifted to higher core temperatures with elevated progesterone + estrogen, but the responsiveness of the vasoconstriction to a given change in skin temperature was not altered (Charkoudian and Johnson, 1999b). Similarly, the shivering response to cold air exposure was shifted to a body temperature about 0.5 °C higher in the mid-luteal phase (Hessemer and Bruck, 1985).

3. Peripheral influences of reproductive hormones

Estrogens increase blood flow in many vascular beds including the peripheral vascular beds (summarized in Fig. 2). In particular, 17β-estradiol (E_2) enhances vasodilation by activating eNOS to rapidly produce NO, as elegantly reviewed by Kim et al. (Kim et al., 2008). Estradiol binds to the endothelial surface membrane estrogen receptor, leading to the initial activation of eNOS. Activated eNOS promotes the production of NO from L-arginine. The NO then diffuses through the endothelial cell caveolae and causes vascular smooth muscle relaxation (Orshal and Khalil, 2004). Thus, estrogens increase endothelium-dependent vasodilation; this may lower the risk of hypertension by decreasing peripheral vascular resistance, and may decrease risk of complications associated with diabetes by increasing peripheral blood flow in some circumstances.

A now classic finding by Kolka and Stephenson demonstrated higher steady-state forearm blood with during exercise at any T_{es} greater than 37.5 °C in the mid-luteal phase of the menstrual cycle, when both estrogens and progesterone are elevated, relative to the early follicular phase, when these hormones are lower (Kolka and Stephenson, 1997). Interestingly, the steady-state vasodilation at higher core temperatures was approximately 40–50% higher during exercise in the luteal phase, likely due to a peripheral effect of estradiol to promote endothelium-dependent vasodilation. An example of the delay in threshold (likely a central effect) and increased steady-state vasodilator response (likely a peripheral effect) are shown in Fig. 1. In terms of net effect on body temperature, this increased steady-state vasodilation did not appear to offset the delayed threshold for vasodilation (noted above), such

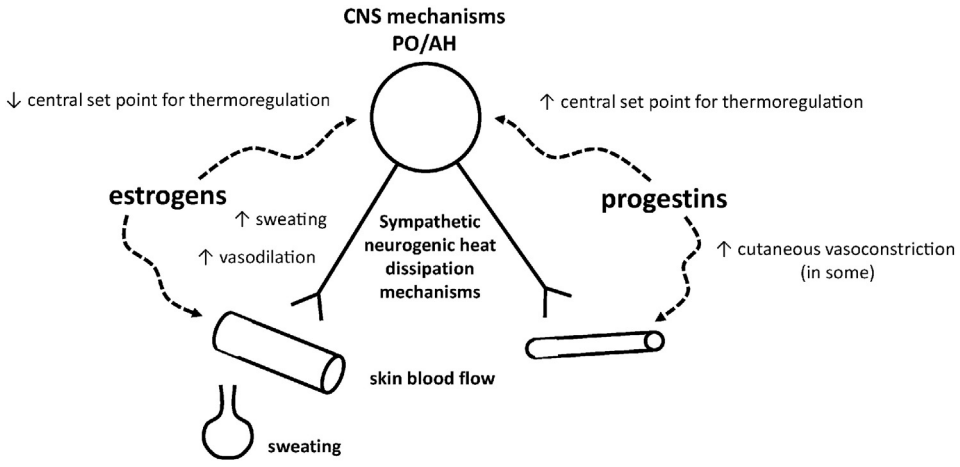

Fig. 2. Schematic summary of influences of female reproductive hormones on thermoregulatory mechanisms in humans. Estrogens tend to lower body temperature by decreasing the central temperature around which hypothalamic thermoregulation occurs. Estrogens also augment peripheral vasodilation by direct vascular influences that augment nitric oxide dependent vasodilation. Progestins tend to cause increases in body temperature and augment peripheral vasoconstrictor responses in a subset of women. Many of the cellular and molecular mechanisms for these integrative influences remain poorly understood. CNS, central nervous system. PO/AH, preoptic/anterior hypothalamus.

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that core temperature remained elevated above the early follicular phase throughout exercise (Kolka and Stephenson, 1997).

In contrast to the vasodilator effects of E_2, progesterone appears to primarily promote vasoconstriction in peripheral microvessels in healthy women. Progesterone was shown to enhance adrenergically controlled cutaneous vasoconstriction in women with normal to high orthostatic tolerance (Wenner et al., 2011). (In this context, the fact that progesterone had little impact on norepinephrine-mediated vascular tone in women with low orthostatic tolerance shows important inter-individual variability in this phenomenon, as a function of [or contributor to] orthostatic tolerance.) Importantly, the effect on adrenergic responses in the women appears to be mediated by cyclooxygenase, supporting a role for prostaglandins in blood pressure regulation in healthy young women (Wenner et al., 2011). Thus, to summarize, both estrogens and progesterone play important roles in mediating changes in peripheral blood flow. Estrogens are usually linked to vasodilation by increasing NO availability from the vascular endothelium through the critical enzyme eNOS. Conversely, progesterone administration increases *vasoconstriction* in some women, a process which appears to be mediated by prostaglandins.

4. Sex differences in thermoregulatory responses

Discussion of influences of female sex hormones on thermoregulation often leads to the question of whether women thermoregulate "better than" or "not as well as" men under various conditions. Historically, some studies have suggested that higher cardiovascular or thermal strain may put women at a disadvantage during exercise in the heat (reviewed in (Charkoudian and Stachenfeld, 2014)). More recently, it has been observed that these differences were largely explained by group differences in body size, fitness and/or acclimation status between the men and women studied (Cheuvront and Haymes, 2001) and environmental conditions, such as relative humidity (Avellini et al., 1980; Cheuvront and Haymes, 2001; Shapiro et al., 1980). Across most activities and environmental conditions, it does not appear that young, healthy women are at any disadvantage when exercising in the heat compared to men of similar age, fitness and overall health.

There do appear to be some differences in sweating rate between men and women when requirements for heat dissipation are very high (Gagnon et al., 2013; Gagnon and Kenny, 2012b, 2011). Gagnon and Kenny performed carefully controlled studies in which they quantitatively evaluated sex differences in thermoregulatory responses to exercise-heat stress while attempting to control for factors such as body size and fitness which may have confounded previous studies (Gagnon and Kenny, 2012b). They compared sweating and skin blood flow responses of men and women exercising at the same overall requirement for heat loss. At the highest exercise intensity, sweating responses were lower in women compared to men, both when measured as overall evaporative heat loss (measured in a whole-body direct calorimeter) and specifically due to differences in sweat gland output. At lower exercise intensities, these differences were not apparent. Skin blood flow responses were not different between groups at any intensity (Gagnon and Kenny, 2012b).

The investigators subsequently evaluated whether sex differences exist in peripheral mechanisms contributing to sweating in humans (Gagnon et al., 2013). Using intradermal microdialysis of acetylcholine and methacholine (which both stimulate sweating), they evaluated peripheral sweat gland responses in men and women. Although, at lower doses, local sweating was similar between groups, women had lower maximal sweating responses to the pharmacological stimulation, suggesting that peripheral mechanisms contribute to lower "maximal" sweating that was observed in women in the prior study (Gagnon and Kenny, 2012b). Taken together, these two studies suggest that, when heat loss requirements (combined metabolic + environmental) are equal, and very high, women have lower sweating rates compared to men. It is important to note that the whole-body heat loss studies were conducted in a chamber set at 40 °C (104 °F) and 12% relative humidity (a very hot, dry, desert-like environment) (Gagnon and Kenny, 2012b). Therefore, although the differences observed were statistically and physiologically significant, it is relatively unlikely that this type of environment would be encountered by most physically active women during normal daily exercise routines. The requirements for heat loss that are more commonly encountered, therefore, are not associated with decreased heat loss in women (compared to men) nor any disadvantage in terms of thermoregulation.

5. Menopause/hot flashes

Menopause is associated with permanent stopping of menstrual periods and ovulation, and typically occurs between the ages of 45–55. Menopause is usually defined as the absence of menstrual bleeding for one year. While menopause is typically associated with aging, early menopause occurs in women who have had ovaries removed. Vasomotor symptoms (VMS), or "hot flashes" are a primary, sometimes disabling, symptom of the period leading up to menopause, called "perimenopause". It is during this time that periods typically become irregular, and menstrual bleeding patterns change. Vasomotor symptoms affect approximately 70% of women in during the menopausal transition. For many women, these VMS continue with less frequency through years into menopause, but most women experience VMS for 1–5 years following the onset of the menopausal transition. Interestingly, there is no current method to predict when vasomotor symptoms will end, and the physiological mechanisms of VMS are poorly understood. The primary feeling associated with a VMS event is a feeling of flushing and sweating, and sometimes dizziness. In some women, VMS are associated with small, transient changes in BP (Low et al., 2008), although these blood pressure changes have not been specifically tied to any symptoms.

In a series of elegant studies, it was demonstrated that changes in skin blood flow during VMS are controlled by similar autonomic mechanisms as contribute to peripheral changes in the thermoregulatory response during peripheral and core temperature heat challenges (Hubing et al., 2010; Low et al., 2008, 2011). For example, the increases in blood flow associated with a VM event have an NO component and appear independent of prostaglandins (Hubing et al., 2010). Earlier studies had suggested that the vasodilation was associated with an unknown circulating substance (Freedman, 2001); however, recent data suggest that that increases in skin blood flow during a VMS are a sympathetic neurogenic event (Low et al., 2011). Low and colleagues measured skin blood flow and skin sympathetic nerve activity in menopausal women during VMS. They compared untreated skin sites to sites treated with botulinum toxin, which blocks cholinergic neurotransmission. The investigators found that cutaneous vasodilation during a VMS was blocked or substantially inhibited by botulinum toxin, and that skin sympathetic nerve activity increased during the VMS. Taken together, these findings provide strong evidence for a neural mechanism for skin blood flow increases during VMS, specifically sympathetic cholinergic in origin (Low et al., 2011). Finally, there is some evidence that exercise training may improve subjective ratings of frequency and intensity of vasomotor events in postmenopausal women (Luoto et al., 2012).

6. Pregnancy

During pregnancy, large fluctuations in female reproductive hormones are associated with longitudinal changes in maternal body temperature throughout gestation. Resting, thermoneutral body temperature increases during the first trimester, then declines throughout the second and third trimesters and after delivery, with a nadir around 12 weeks post-partum (Hartgill et al., 2011). Although these changes are not well studied, they are likely to be related to both the thermoregulatory influences of progesterone, and the overall increases in

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estrogens later in pregnancy. Progesterone and estrogens, when elevated together (such as in the luteal phase of the menstrual cycle), are associated with increases in body temperature (Charkoudian and Johnson, 1999a; Stephenson and Kolka, 1985). These combined hormones likely contribute to the increases in body temperature seen during the first trimester of pregnancy. Large increases in estrogens (with relatively low progesterone levels) during the second and third trimesters may contribute to increased peripheral blood flow (Brooks et al., 1997) and lower body temperatures (Stephenson and Kolka, 1999). Exercise thermoregulation is similarly altered during the course of pregnancy, such that core temperature during exercise decreases progressively during the second and third trimesters (Clapp, 1991). These changes likely protect the developing fetus from excessive hyperthermia during maternal exertion.

7. Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrinopathy in young women, affecting 6%–10% of reproductive-age women, and is the most common cause of infertility (Tsilchorozidou et al., 2004). A sedentary lifestyle and high-fat diet have emerged as primary environmental risk factors for PCOS (Diamanti-Kandarakis and Dunaif, 2012; Flanagan et al., 2008). This latter point is particularly emphasized by the fact that physical activity *independent of weight loss* improves insulin sensitivity, reduces serum levels of androstenedione and dehydroepiandrosterone (DHEA) (Harrison et al., 2011; Hutchison et al., 2011) and improves reproductive function in PCOS (Harrison et al., 2011). Exercise is routinely prescribed for women with PCOS to induce weight loss and improve insulin resistance (Moran et al., 2006). However, compliance with these prescriptions and participation in exercise programs in women with PCOS remains low, and little information on the efficacy of specific programs for treating PCOS exist. Obese women with PCOS regulate temperature adequately during exercise in the heat, maintaining similar core temperature to obese women without PCOS (Stachenfeld et al., 2010). Interestingly, women with PCOS maintained core temperature during exercise in heat with higher sweating rates, even at mild exercise intensity, relative to control obese subjects (Stachenfeld et al., 2010). The exercise intensity in these sessions was light and elicited a very low sweating rate in the obese subjects without PCOS. However, the women with PCOS sweated earlier and more profusely relative to women without PCOS and this greater water loss was independent of obesity. Finally, although estradiol administration increased sweating in the control women, women with PCOS were insensitive to changes in estradiol exposure, with or without testosterone (Stachenfeld et al., 2010). Importantly, to date, despite the important of exercise and physical activity in treating PCOS no specific exercise guidelines for women with PCOS have been established. Based on these recent findings, it appears that special attention should be paid to hydration during longer exercise periods, even in mild heat. PCOS may have more of a tendency to become dehydrated because of their elevated sweating rates.

8. Summary and future directions

Over the past three decades, much progress has been made in the study of physiological influences of female reproductive hormones on thermoregulation at rest and during exercise. In terms of autonomic mechanisms, both central and peripheral vascular effects of these hormones contribute to their net influences on body temperature and its regulation. The influences of estrogens and progestins on integrative thermoregulatory mechanisms are summarized schematically in Fig. 2. Estrogens tend to promote heat dissipation and lower body temperatures, whereas progesterone tends to cause an increase in body temperature. Central (hypothalamic) effects of estrogens include activation of sympathetic heat dissipation pathways (cutaneous vasodilation and sweating). Peripheral vascular influences include promotion of heat dissipation via nitric oxide-dependent vasodilation. In contrast, progesterone tends to shift central control of body temperature to higher temperatures, and can promote vasoconstriction in the peripheral vasculature. Many aspects of the interactions between female hormones and temperature regulation remain poorly understood. For example, the cellular and molecular mechanisms by which estrogens or progesterone (or androgens, in the case of PCOS or transgender/transsexual individuals) impact autonomic control of thermoregulation remain poorly studied. Imaging and spectroscopic methods may allow less invasive approaches to explore these questions in the future. Further, while much of our focus has been on the autonomic responses to environmental exposures such as heat or cold, we can begin to explore how heat or cold may be harnessed to improve health. One possibility may be studies examining the potential thermoregulatory links between sympathetically-mediated brown fat and muscle metabolism and integrative regulation of blood glucose levels. These represent important areas for future study.

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