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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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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