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Review

Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages

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Summary

Vasomotor symptoms (VMS), commonly called hot flashes or flushes (HFs) and night sweats, are the menopausal symptoms for which women seek treatment during menopause most often. VMS are a form of temperature dysfunction that occurs due to changes in gonadal hormones. Normally, core body temperature (CBT) remains within a specific range, oscillating with daily circadian rhythms. Physiological processes that conserve and dissipate heat are responsible for maintaining CBT, and tight regulation is important for maintenance of optimal internal organ function. Disruption of this tightly controlled temperature circuit results in exaggerated heat-loss responses and presents as VMS. The mechanistic role related to changes in gonadal hormones associated with VMS is not understood. Hormone therapy is the most effective treatment for VMS and other menopausal symptoms. Estrogens are known potent neuromodulators of numerous neuronal circuits throughout the central nervous system. Changing estrogen levels during menopause may impact multiple components involved in maintaining temperature homeostasis. Understanding the pathways and mechanisms involved in temperature regulation, probable causes of thermoregulatory dysfunction, and "brain adaptation" will guide drug discovery efforts. This review considers the processes and pathways involved in normal temperature regulation and the impact of fluctuating and declining hormones that result in VMS during the menopausal transition.

Keywords: Temperature; estrogen; woman

Introduction

At some time during the menopausal transition, as many as 80% of women will experience the classic menopausal vasomotor symptoms (VMS), hot flashes or flushes (HFs) and night sweats (National Institutes of Health 2005a). These symptoms can start to occur in the perimenopausal period (Soules et al. 2001), a stage of hormonal fluctuation that leads up to menopause (1 year after the last menstrual cycle), and can last throughout the postmenopausal phase (Rödström et al. 2002). Hot flushes and night sweats vary greatly in intensity, both between women and within individual women, over time. Mild HFs are experienced as a transient warming sensation, while severe symptoms may include sudden and intense heat spreading over the upper body and face, reddening of the skin or flushing, and severe perspiration. In one survey, more than half of the symptomatic women reported that flushing was followed by chills and shivering (Kronenberg 1990). Other symptoms associated with HF episodes include pressure in the head or chest, anxiety, nausea, and changes in heart rate and breathing. Night sweats are HFs that occur with heavy perspiration during sleep and cause sleep disruption (Woodward and Freedman 1994). Additionally, VMS may cause an increase in vulnerability in some women, to other physical (somatic) (Dugan et al. 2006; Kronenberg 1999) and psychological (mood disturbance) (Joffe et al. 2002) symptoms that result in a reduced quality of life and diminished work production (Utian 2005). Hot flush episodes generally last 1–5 min, although a small percentage of women report flushes

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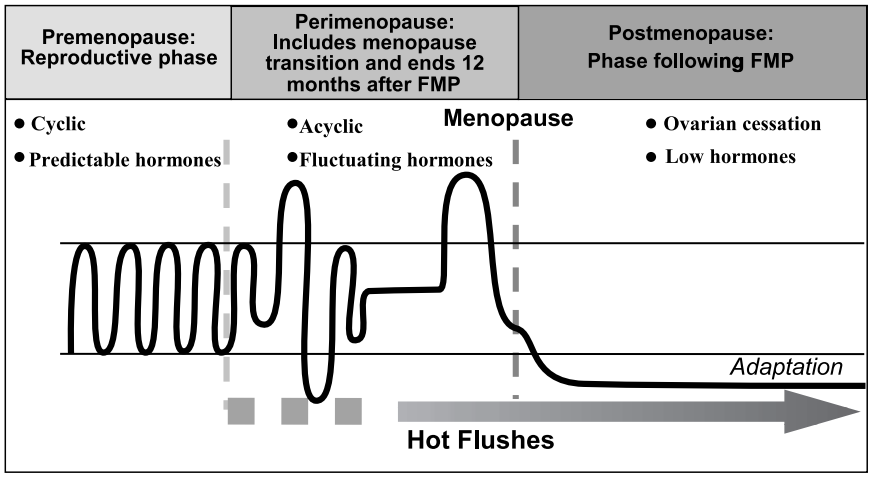

Fig. 1. Relationship between estrogen and a woman's reproductive phases and the occurrence of hot flushes. The reproductive phase is characterized by cyclic and predictable estrogen levels. During perimenopause, hormones fluctuate and become acyclic. During this period, many women experience VMS; although severe, the frequency is transient. During the postmenopausal period, women can experience severe and persistent VMS due to the declining levels of ovarian hormones. For most women, VMS eventually diminish over time. *FMP* final menstrual period

lasting up to 15 min (Kronenberg 1990). These VMS are associated with the fluctuating and eventual decline of ovarian hormone levels during and following the menopausal transition. They also occur in cancer survivors such as women with loss of ovarian function due to breast cancer treatment (Mom et al. 2006) and men who have undergone androgen ablation therapy (Holzbeierlein et al. 2003).

Changing estrogen levels play a role in the onset of VMS. Estrogen therapy has been shown to relieve VMS, reducing the number of HFs by as much as 95% in menopausal women (Baerug et al. 1998). In addition, many women who experience an abrupt onset of menopause brought on by oophorectomy have more severe symptoms than women who go through a natural, gradual transition (Hendrix 2005). Whether there is a direct relationship between circulating estrogen levels and the prevalence of HFs remains controversial (Øverlie et al. 2002; Randolph et al. 2005); the occurrence of VMS appears to be associated with the unpredictable fluctuations in estrogen levels occurring during the perimenopausal period as well as the diminished levels after menopause (Berendsen 2000; Freedman 2001; Deecher 2005) (Fig. 1). According to a study of 1400 women older than 25 years, women start reporting HFs as early as 38 years of age, while cycles are still predictable, suggesting that changes in ovarian function have started to occur (Rödström et al. 2002). These symptoms peak in late perimenopause or early menopause (average age, 52–54 years) and coincide with the final menstrual period (FMP) (Rödström et al. 2002; National Institutes of Health 2005a). For most women, HFs and night sweats eventually diminish in frequency and severity in the postmenopausal period (Guthrie et al. 2004; Avis et al. 2005) but for some women, VMS may last throughout the rest of their lifetime (Rödström et al. 2002).

VMS are believed to result from a dysfunction in the tightly controlled temperature circuitry leading to an exaggerated activation of heat dissipation responses, including peripheral vasodilation and sweating. Although in this review, the focus is on gonadal hormone-induced VMS, specific diseases, medications and neuronal damage can also cause thermoregulatory dysfunction. In brief, this important thermoregulatory circuitry is made up of 3 main components: the brain, the internal body cavity, and the peripheral vasculature (Deecher 2005). These components work together to maintain temperature homeostasis. In addition, other thermoregulatory zones provide temperature inputs. The body's various thermoregulatory zones send temperature signals to the corresponding thermoregulatory centers in the brain, particularly the hypothalamus. These centers use the signals to maintain optimal core body temperature (CBT) by inducing vasodilation to dissipate heat or vasoconstriction to conserve heat. Thus, an HF is a rapid, exaggerated response causing an intense heat sensation (flash), upper body skin reddening (flush), and increased skin blood flow resulting in changes in heart rate and blood pressure. It is hypothesized that the body is not really in a ''hyperthermic'' state, but that there is a miscommunication in temperature signaling that regulates normal temperature responses. Therefore, the message to rapidly reduce CBT results in extreme vasodilation followed by sweating and in some cases drenching

perspiration, especially at night, which can lead to sleep disruption (Kronenberg 1990; North American Menopause Society 2004a). Often, the extreme heat loss caused by the vasodilation of blood vessels results in chills and shivering as the body attempts to compensate for the loss (Freedman 2001).

Hormone therapy (HT) has long been the standard treatment for HFs and night sweats (North American Menopause Society 2004b); however, there is an unmet need for a safe and effective nonhormonal treatment for VMS to complement existing approved therapies (National Institutes of Health 2005b). In order to address this need, the underlying pathophysiology of VMS and the potential pathways, mechanisms, and targets involved in temperature regulation must be understood. This paper discusses normal thermoregulatory function and the impact of fluctuating and declining hormone levels that result in VMS during and following the menopausal transition.

Thermal homeostasis and regulation

Temperature homeostasis is a dynamic state of stability between an animal's internal and external environments. When functioning properly, the thermoregulatory system monitors and maintains CBT within a specific range required for optimal organ integrity and function regardless of environmental temperatures. When CBT falls below the optimal range required for maintenance of normal organ function, peripheral vasoconstriction and shivering are initiated to conserve body heat and raise internal temperature (Fig. 2). When it exceeds the optimal range, peripheral vasodilation and sweating are triggered and excess heat is dissipated through the skin by radiation and evaporative cooling processes (Charkoudian 2003). These 2 thresholds, the upper (sweating) threshold which triggers heat loss and the lower (shivering) threshold which triggers heat conservation or generation, define the thermoneutral zone (Cabanac and Massonnet 1977). The core temperature thermoneutral zone is maintained within defined (preset) limits that vary over the circadian cycle (Hensel 1973; Deecher 2005).

Temperature regulation is a complex, highly regulated, and integrated network of neuroendocrine, autonomic, and somatomotor responses (Deecher 2005). The temperature circuitry is a bidirectional feedback loop that communicates between 3 major communication centers. The 3 major components involved in thermoregulatory function (Fig. 3) consist of afferent thermosensitive pathways that provide information about CBT,

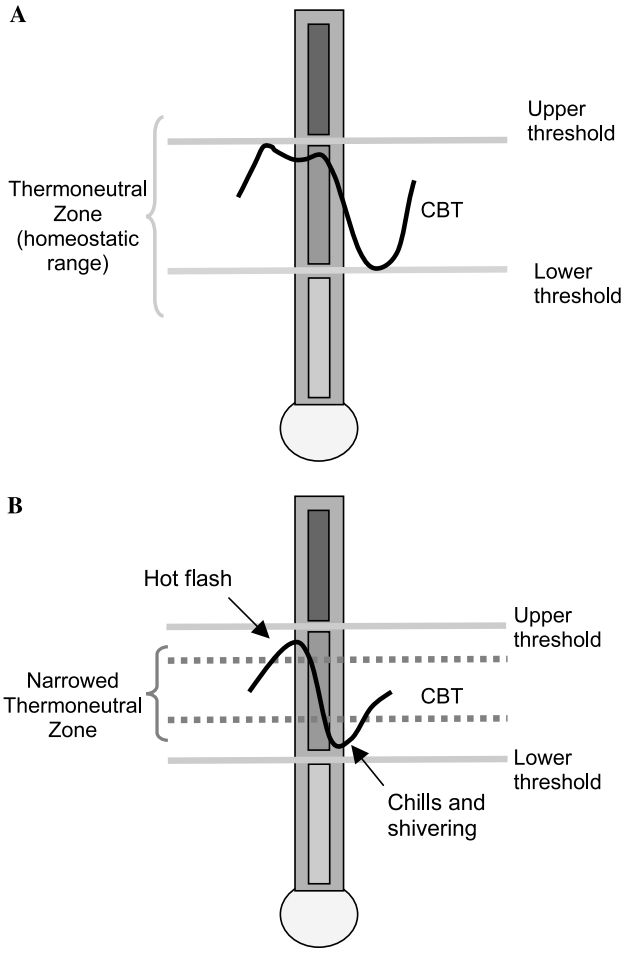

Fig. 2. Maintenance of core body temperature (CBT) is critical to organ integrity and optimal function (Deecher 2005). It has been hypothesized that core temperature is regulated between an upper threshold for sweating (heat dissipation) and a lower threshold for shivering (heat generation). Within the thermoneutral zone, major thermoregulatory responses such as sweating and shivering do not occur. These mechanisms maintain temperatures within the designated thresholds (Freedman 2005). **A** Normal temperature regulation. **B** Dysfunctional temperature regulation

central processing areas in the central nervous system (CNS), and peripheral vasculature, which receives efferent signals controlling thermoregulatory responses. Changes in CBT are communicated to the brain by heat- and cold-sensitive fibers in the CNS (Boulant 1998), deep body tissues, and skin (Boulant and Gonzalez 1977). Deep body temperature sensors are located in the gastrointestinal tract and other internal organs, intra-abdominal veins, and the spinal cord (Simon 2000; Romanovsky 2007). Thermosensitive nerve fibers from skin and deep tissues both contribute to generating thermoregulatory responses (Frank et al. 1999).

Integration of temperature information occurs at multiple levels in the CNS, but the hypothalamus, specifically the anterior hypothalamus/preoptic area (POA), is

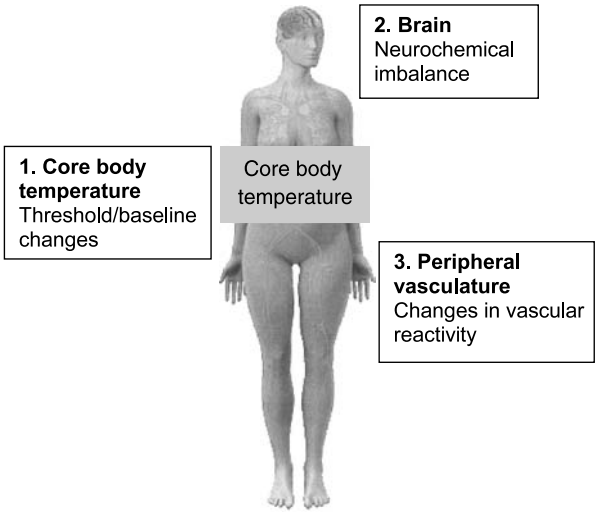

Fig. 3. The 3 major components involved in thermoregulatory function include afferent thermosensitive pathways providing information about core body temperature (CBT); central processing areas in the CNS; and peripheral vasculature, which receives efferent signals controlling vasodilation and vasoconstriction. Dysregulation at one or more of these sites can result in miscommunication and impaired temperature regulation. Figure reproduced from Deecher (2005) with modifications

considered to be the major CNS thermoregulatory processing center (Crawshaw et al. 1985; Romanovsky 2007). The POA projects to multiple effectors in the brainstem and spinal cord via the medial forebrain bundle (Boulant 2000). Warm-sensitive neurons in the POA appear to exert control over heat-loss effectors located in the lateral hypothalamus, periaqueductal grey matter, and reticular formation (Zhang et al. 1997), which are responsible for peripheral vasodilation and sweating (Bruck and Zeisberger 1990; Boulant 2000).

The primary mechanisms for regulating CBT are changes in blood flow through the skin and subcutaneous area and sweating. Peripheral vasculature receives sympathetic input controlling both vasodilation and vasoconstriction responses (Charkoudian 2003). Thus, when CBT rises above the required maintenance preset limits, peripheral vasodilation is triggered, resulting in increased blood flow to peripheral blood vessels. Conversely, when the temperature drops below the CBT preset limits, reduced blood flow in the peripheral blood vessels occurs as a means of retaining heat in the body (Charkoudian 2003). Chills and shivering may follow an HF or night sweat episode in order to regenerate excessive heat loss and reestablish normal CBT.

Multiple levels of thermoregulatory neural circuitry, central and peripheral, are under catecholinergic and/or serotonergic control. Serotonergic cells from the dorsal raphe nucleus (DRN) of the brainstem project to the POA, where mRNA for pre- and postsynaptic serotonin (5-HT) receptors have been localized in nonhuman primates (Gundlah et al. 1999; Bethea et al. 2002). The POA is also a target for norepinephrine (NE) pathways. The POA receives NE input from the nucleus of the solitary tract and the locus coeruleus. The existence of an α-adrenoceptor mRNA and β-adrenergic receptor activation have been demonstrated in the POA and hypothalamus (Petitti and Etgen 1990; Karkanias et al. 1996, 1997). Vasomotor effectors controlling peripheral vasodilation and vasoconstriction are also modulated by noradrenergic and serotonergic input (Martin 1994; Abdelmawla et al. 1999).

Thermoregulatory dysfunction

Thermoregulatory dysfunction appears to result from a disruption or miscommunication in the complex signaling and information processing between CBT, brain, and peripheral vasculature. Such disruptions might occur at one or more of these levels, and can have a variety of possible causes, including disease states, drug-induced effects, and gonadal hormone changes. Damage to CNS structures, particularly the hypothalamus, from injury or disease can disrupt temperature homeostasis. Significant changes in thresholds for thermoregulatory responses are associated with lesions to the hypothalamus in patients with multiple sclerosis (Sullivan et al. 1987; Edwards et al. 1996; White et al. 1996; Kurz et al. 1998) and traumatic brain injury, which when associated with damage to the hypothalamus (Crompton 1971), can result in posttraumatic hyperthermia (Thompson et al. 2003).

A commonly recognized example of thermoregulatory dysfunction is VMS associated with menopause. However, VMS are also reported by other patients that are not menopausal but, in some cases, are associated with changes in levels of circulating gonadal hormones or specific drug interactions with estrogen receptors (i.e., raloxifene, tamoxifen) (Land et al. 2006; Jordan 2007). For example, women with a history of breast cancer often experience VMS, as common chemotherapeutic agents may cause premature ovarian failure resulting in abrupt ovarian hormone level decline. In addition, these women may have been placed on an anti-estrogenic agent as a cancer preventative such as tamoxifen (Land et al. 2006) and aromatase inhibitors (Mom et al. 2006). Hot flushes are also experienced by men who receive androgen ablation or androgen deprivation therapy for prostate cancer, treatments that dramatically lower plasma testosterone levels, which, in

turn, lower available brain estrogen from aromatization (Holzbeierlein et al. 2003).

Thermoregulatory dysfunction associated with menopause

Years before the FMP, ovarian function begins to decline and estrogen levels fluctuate dramatically (Rödström et al. 2002; Bachmann 2005; Santoro 2005). In a review of studies documenting hormonal changes through the menopausal transition, Burger and colleagues (2002) concluded, ''The most-noteworthy characteristic of the perimenopause stage is significant hormonal variability.'' Burger et al. (2002) cited several studies in which perimenopausal estradiol (a major endogenous human estrogen) levels or excretion patterns were characterized by large variations characteristic of abrupt increases or decreases. Santoro and colleagues (1996) showed that women in the menopausal transition had periods of anovulatory cycles and periods of time when urine estrogen metabolite (estrone) levels almost double the premenopausal stage concentrations. They also demonstrated that during this perimenopausal period, women may experience acyclic intervals with low, tonic estradiol levels characteristic of postmenopause. This unpredictable period of estrogen instability is thought to contribute (directly or indirectly) to a variety of menopausal complaints, including physical (VMS, sleep disturbances, urogenital complaints [Nelson et al. 2005]), psychological (irritability, depressive symptoms, mood disturbances, low libido [Dennerstein et al. 1994; Cohen et al. 2006; Freeman et al. 2006]), and somatic (aches and pains, fatigue [Shaver and Paulsen 1993]) symptoms.

The precise mechanisms underlying the pathophysiology of VMS are unknown, but there are at least 3 proposed hypotheses that have been studied. Various elements of these proposed hypotheses may contribute, in part, to this thermoregulatory dysfunction. The most prominent hypothesis, initially proposed by Tataryn et al. (1980), is that there is a change in the predefined acceptable temperature limits (thermoregulatory set points) or a miscommunication of these set points. A narrowing of this thermoneutral zone may occur, such that small, normally insignificant elevations in CBT signal a heat dissipation response, triggering an exaggerated reaction, i.e., hot flush (Freedman 2005) (Fig. 3). Freedman and his colleagues have carried out a series of experiments addressing this hypothesis (Freedman et al. 1995; Freedman and Woodward 1995, 1996; Freedman and Krell 1999; Freedman 2001). In these studies, they examined the relationship between CBT and the onset of heat-loss and heat-conserving responses. Core body temperature was measured in symptomatic and asymptomatic menopausal women using radiotelemetry pills. The subjects were warmed or cooled and thresholds for shivering and sweating were determined. The results of the experiments indicated that the shivering threshold is raised (Freedman and Krell 1995) and the sweating threshold is lowered (Freedman and Krell 1999), such that the normally acceptable temperature limit (thermoregulatory neutral zone) is significantly narrowed, from the normal 0.4 °C to ''virtually nonexistent'', in symptomatic menopausal women (Freedman and Krell 1996; Freedman 2001). Studies further indicated that HFs are, in most cases, preceded by small increases in CBT (Freedman et al. 1995; Freedman and Woodward 1996). Warming studies demonstrated that raising CBT slightly will trigger sweating and vasodilation in menopausal women with VMS but not asymptomatic menopausal women (Freedman 2001). Thus, in symptomatic menopausal women, small changes in CBT that would be tolerated under normal physiological circumstances now trigger anomalous heat dissipation responses (Freedman and Krell 1999), such as the extreme vasodilation and sweating reported by women with VMS associated with menopause.

A second hypothesis regarding the cause of VMS is related to the loss of responsiveness of the peripheral vasculature. Responses to thermal challenges in skin circulation are vital to normal thermoregulation, involving a feedback loop to and from the vasculature in order to respond to changes in internal body temperature (Charkoudian 2003).

It has been postulated that disturbances in local and reflex thermoregulatory control of skin circulation may contribute to thermoregulatory dysfunction. Changes in vascular reactivity may interfere with the ability of blood vessels to respond rapidly and to the appropriate degree, resulting in an exaggerated response (Charkoudian 2003). The occurrence of VMS may, in part, be due to a delay in the vasculature's response to messages arising at the level of the internal cavity sending signals that the temperature is too high and needs to be decreased. Estrogen and progesterone both appear to influence skin blood flow control (Brooks et al. 1997). The fluctuations in estradiol levels that occur during perimenopause may affect vascular reactivity responsiveness by altering the threshold for cutaneous vasodilation. The low levels of estradiol during the postmenopausal period may contribute to the reduced elasticity of the blood vessels, resulting in delayed responses due to

changes in internal body temperature (Joswig et al. 1999).

Another area of research that has been postulated to contribute to the pathophysiology of VMS is neurochemical alterations caused by changes in gonadal hormones during the menopausal transition period (Shanafelt et al. 2002). Numerous clinical trials assessing the efficacy of various centrally acting compounds have been conducted (Nelson et al. 2006a). Anticholinergic drugs have been experimentally tested based on the notion that the cholinergic system was involved in the dysfunction (Clayden 1972; Williams 1973; Clayden et al. 1974). Other agents such as clonidine (an alpha-2 adrenergic agonist) and gabapentin have been used with some success (North American Menopause Society 2004a; Deecher 2005; Nelson et al. 2006a). Additionally, the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have also shown some effect in reducing VMS (Nelson et al. 2006b). These drugs are proposed to work by ''restoring'' altered levels of 5-HT and/or NE that are believed to be affected due to the loss of modulation by estrogens (Deecher et al. 2007). The efficacy of these compounds provides some support to the hypothesis that neurochemical imbalances in the brain may be an underlying cause of the thermoregulatory dysfunction that results in VMS associated with gonadal hormone changes.

Estrogens as neuromodulators

Estrogens are potent neuromodulators known to regulate the structure and function of numerous neuronal circuits throughout the CNS (Gould et al. 1990; Woolley and McEwen 1993; McEwen and Alves 1999; McEwen 2001; Genazzani et al. 2007). Over the course of the human life span, the female brain must respond and adapt to changes in estradiol levels dependent on her life stage. Although puberty requires that both male and female brains adapt to a new hormonal environment, the cyclic and transient hormonal fluctuations of the female menstrual cycle may require a very different capacity of flexibility and functional responsiveness. During the reproductive years, the female brain must develop flexible and responsive mechanisms due to cyclic and synchronized changes in neuroendocrine input in order to maintain precisely timed ovulatory events. During the menopausal transition, these timed cycles become asynchronized and unpredictable resulting in ovarian hormone levels being exaggerated (Santoro et al. 1996) (Fig. 1), demanding even greater flexibility in neuronal responsiveness (Gibbs 1998; McEwen 2001). This period of the life cycle could be considered a time of unpredictable hormonal messaging. Thus, the brain and the neurochemical mechanisms responsible for maintaining homeostasis are unable to adjust rapidly or efficiently to optimally function. It is hypothesized that after menopause, the female brain must adapt to the absence of cyclic levels of ovarian hormones and establish a new baseline of homeostasis in order to maintain normal brain function (Birge 2003). The inability to respond or establish a new baseline of neuronal function could lead to increased susceptibility to brain-related dysfunctions including thermoregulatory dysfunctions.

Therefore, unexpected changes in estrogen levels during the menopausal transition may impact multiple components involved in maintaining temperature homeostasis. Estrogens have been shown to control gene expression, up- or downregulating numerous components of cell signaling pathways, including membrane receptor proteins, transporters, and enzymes involved in synthesis or degradation of neurotransmitters, as well as directly altering neuron membrane currents and firing patterns (McEwen and Alves 1999; Bethea et al. 2000a; McEwen 2002). Unpredictable fluctuations and the decline of gonadal hormones are believed to affect neural systems regulated by estrogens. The hypothalamus will be particularly affected by these changes in gonadal hormones since it is highly hormone-responsive due to the expression of both estrogen and progesterone receptors (Gould et al. 1990; Woolley and McEwen 1993; McEwen 2001; McEwen and Alves 1999). This region of the brain is also considered a key site for integration of thermal information and control of thermoregulatory responses (Boulant 2000). Decreasing hormone levels may lead to diminished neuronal function resulting in a change in the balance of key neurotransmitters involved in temperature regulation such as 5-HT and NE.

Estrogens may modulate any level of the thermoregulatory pathway. However, there is a wealth of evidence that the hypothalamus, and specifically the POA, is hormone responsive, and that estrogen may regulate the functional activity of neurotransmitter systems within the POA. Estrogen receptors have been localized in regions associated with the thermoregulatory system (Bethea et al. 1996; Gundlah et al. 2000; Osterlund et al. 2000), indicating that those areas may be responsive to estrogen and that their structure or function may be influenced by changes in estrogen levels, as during

the menopausal transition. There is supporting in vitro and in vivo preclinical evidence that estrogens are neuromodulators of the serotonergic and noradrenergic systems that are believed to play a role in the maintenance of temperature regulation in the brain as well as the periphery. Various animal reports have shown that estrogen receptors are expressed in both NE and 5-HT projections to the hypothalamus (Kalló et al. 1992; Bethea et al. 2000a; Lu et al. 2001; Temel et al. 2002), and that estrogens can regulate both serotonergic and noradrenergic systems by modulating production, release, recycling/elimination, and receptor activity (Shanafelt et al. 2002; Bachmann 2005).

The effects of fluctuating estrogen levels on NE and 5-HT have been examined specifically with respect to thermoregulatory function in animal models (Maswood et al. 2006; Deecher et al. 2007), and modulation of these neurotransmitter systems in the POA have been studied in the context of other functions as well. Estrogens have been reported to influence 5-HT and NE synthesis, density of pre- and postsynaptic binding sites, and deactivation via neurotransmitter reuptake and degradation (Genazzani et al. 1997; Bethea et al. 1998, 2002; McEwen and Alves 1999; Herbison et al. 2000; Etgen et al. 2001; Amin et al. 2005). Estrogens appear to increase the availability of 5-HT by boosting the capacity to synthesize the transmitter and by slowing its degradation (Pecins-Thompson et al. 1996; Bethea et al. 2000b; Gundlah et al. 2002, 2005; Hiroi et al. 2005; Sanchez et al. 2005). It also regulates 5-HT receptor density and binding and slows the transmitter's removal from the synapse (Lu and Bethea 2002; Le Saux and Di Paolo 2005). Using both in vitro and in vivo techniques, estrogens have been shown to modulate the noradrenergic system in ways similar to those demonstrated for 5-HT, with affects on synthesis (Serova et al. 2002, 2004) and degradation (Gundlah et al. 2002), as well as downstream receptor signaling and function (Karkanias and Etgen 1994).

Such estrogen-associated modulations of NE and 5-HT signaling have been proposed to be one means by which thermoregulatory dysfunction occurs due to hormonal changes (Deecher et al. 2007). Thus, fluctuations in estrogen levels during the menopausal transition are hypothesized to disrupt the normal balance of NE and 5-HT maintained under cyclic estrogen control, thereby altering downstream signaling in thermoregulatory circuits as well as other neurologically important pathways. Clinical trial results also support the hypothesis that 5-HT and NE may play an important role in thermoregulation showing that SSRIs or SNRIs can alleviate VMS, reducing HF scores by up to 65% (Loprinzi et al. 2000, 2002; Stearns et al. 2003, 2005), although it should be noted, new clinical reporting is suggesting that increasing 5-HT alone may not be adequate to alleviate VMS (Suvanto-Luukkonen et al. 2005; Grady et al. 2007). Moreover, research shows that plasma NE levels are elevated before and during HFs, and that production and release of NE in the hypothalamus is inhibited by metabolic by-products of estrogen (Freedman and Krell 1999; Shanafelt et al. 2002).

Taken together, in vitro and in vivo preclinical data with clinical findings support the hypothesis that changes in estrogen levels impact important neurochemical processes involved in temperature regulation.

Adaptation to gonadal hormone changes

As mentioned earlier, VMS have their onset in the early perimenopausal period (Rödström et al. 2002). During the perimenopausal period, the occurrence of VMS is transient yet severe, due to the irregularity and unpredictability of hormone levels (Burger 1996). These symptoms diminish over time in the postmenopausal period, although some women report these symptoms long after the last menstrual cycle (Rödström et al. 2002). The slow progression of the reduction and eventual disappearance of VMS suggests that over time the brain must ''reset'' or ''adapt'' to a different neurochemical level in order to restore normal temperature regulation. It appears this adaptation period is individually determined and can require a rather extended amount of time to readapt brain function, reset temperature thresholds, and return to normal temperature responses. Evidence suggests that estradiol is the primary gonadal hormone responsible for VMS and when given to women, estrogens have been shown to alleviate these symptoms. For the majority of women taking HT to treat menopausal VMS, the symptoms recur after cessation of HT, suggesting that VMS are relieved but not eliminated (Haimov-Kochman et al. 2006; Ness et al. 2006). This suggests that there is a period of time during which brain function must reset and adjust to the ''hypoestrogenic'' state after menopause and this process is referred to as ''brain adaptation''. The idea of ''brain adaptation'' supports the hypothesis that changes in neurochemical processes are involved in thermoregulatory dysfunction. Most women adapt to this new ''hypoestrogenic'' state, although there are individual differences in the degree and duration of suffering before adaptation is complete. It should be noted that some women will experience

VMS throughout their remaining life span (Rödström et al. 2002).

Conclusions

Thermoregulatory dysfunction appears to result from a miscommunication in the complex signaling and information processing between the CBT, brain, and vascular system. VMS, commonly referred to as hot flashes or flushes and night sweats, are extreme thermoregulatory responses resulting from a disruption in the ability to keep body temperature within a specific optimal range. The incidence of VMS has been reported by up to 80% of all women advancing through menopause, with symptoms diminishing over time in the postmenopausal period. The slow progressive lessening and eventual disappearance of VMS suggest that over time the brain must ''reset'' or ''adapt'' to different neurochemical levels in order to restore normal temperature regulation. This period of ''brain adaptation'' may be a key element to study in order to further understand the pathophysiology of thermoregulatory dysfunction and develop effective nonhormonal therapies for VMS associated with menopause.

A direct relationship between plasma estradiol levels and the occurrence of VMS has not been unequivocally demonstrated (Øverlie et al. 2002; Randolph et al. 2005), but the dramatic fluctuations in hormone levels during the perimenopausal transition and the declining levels of estradiol overall in postmenopause are thought to disrupt central thermoregulatory processing, perhaps via interactions with the neurotransmitter systems important to temperature control. The POA of the hypothalamus, believed to be the main central processing area for temperature regulation, is also a site of estrogen sensitivity. The NE and 5-HT signaling pathways in the POA, both critical to thermoregulatory processing, are thought to be affected by estrogen changes. It is hypothesized that fluctuating and declining hormone levels modulate key neurotransmitters and the expression or function of their receptors, thereby altering the response patterns of the thermoregulatory circuits and changing the thresholds for sweating and shivering responses. This hypothesis predicts that agents that stabilize NE and 5-HT could alleviate VMS, and in several clinical trials 5-HT and NE modulators have been shown to be effective. It is important to note that there is reciprocal feedback between noradrenergic and serotonergic neurons, with each system ultimately influencing the activity of both neurotransmitters (Guyton and Hall 2006). Recent negative results from a placebo-controlled trial of the SSRIs citalopram and fluoxetine (Suvanto-Luukkonen et al. 2005) suggest modulation of 5-HT alone is not sufficient to alleviate VMS, and agents that contain both 5-HT and NE activity (i.e., SNRIs) may be necessary for effective therapy (Loprinzi et al. 2000).

References

Abdelmawla AH, Langley RW, Szabadi E, Bradshaw CM (1999) Comparison of the effects of venlafaxine, desipramine, and paroxetine on noradrenaline- and methoxamine-evoked constriction of the dorsal hand vein. Br J Clin Pharmacol 48: 345–354

Amin Z, Canli T, Epperson CN (2005) Effect of estrogen-serotonin interactions on mood and cognition. Behav Cogn Neurosci Rev 4: 43–58

Avis NE, Brockwell S, Colvin A (2005) A universal menopausal syndrome? Am J Med 118 (Suppl 12B): 37–46

Bachmann GA (2005) Menopausal vasomotor symptoms: a review of causes, effects and evidence-based treatment options. J Reprod Med 50: 155–165

Baerug U, Winge T, Nordland G, Faber-Swensson E, Heldaas K, Norling B, Larsen S, Arce JC (1998) Do combinations of 1 mg estradiol and low doses of NETA effectively control menopausal symptoms? Climacteric 1: 219–228

Berendsen HHG (2000) The role of serotonin in hot flushes. Maturitas 36: 155–164

Bethea CL, Brown NA, Kohama SG (1996) Steroid regulation of estrogen and progestin receptor messenger ribonucleic acid in monkey hypothalamus and pituitary. Endocrinology 137: 4372–4383

Bethea CL, Pecins-Thompson M, Schutzer WE, Gundlah C, Lu ZN (1998) Ovarian steroids and serotonin neural function. Mol Neurobiol 18: 87–123

Bethea CL, Gundlah C, Mirkes SJ (2000a) Ovarian steroid action in the serotonin neural system of macaques. Novartis Found Symp 230: 112–130

Bethea CL, Mirkes SJ, Shively CA, Adams MR (2000b) Steroid regulation of tryptophan hydroxylase protein in the dorsal raphe of macaques. Biol Psychiatry 47: 562–576

Bethea CL, Lu NZ, Gundlah C, Streicher JM (2002) Diverse actions of ovarian steroids in the serotonin neural system. Front Neuroendocrinol 23: 41–100

Birge SJ (2003) Estrogen and the brain: implications for menopause management. In: Schneider HPG (ed) Menopause: the state of the art – in research and practice. Parthenon, New York, pp 191–195

Boulant JA (1998) Hypothalamic neurons. Mechanisms of sensitivity to temperature. Ann N Y Acad Sci 856: 108–115

Boulant JA (2000) Role of the preoptic-anterior hypothalamus in thermoregulation and fever. Clin Infect Dis 31 (Suppl 5): S157–S161

Boulant JA, Gonzalez RR (1977) The effect of skin temperature on the hypothalamic control of heat loss and heat production. Brain Res 120: 367–372

Brooks EM, Morgan AL, Pierzga JM, Wladkowski SL, O'Gorman JT, Derr JA, Kenney WL (1997) Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. J Appl Physiol 83: 477–484

Bruck K, Zeisberger E (1990) Adaptive changes in thermoregulation and their neuropharmacological basis. In: Schonbaum E, Lomax P (eds) Thermoregulation: physiology and biochemistry. Pergamon, New York, pp 255–307

Burger HG (1996) The endocrinology of the menopause. Maturitas 23: 129–136

Burger HG, Dudley EC, Robertson DM, Dennerstein L (2002) Hormonal changes in the menopause transition. Recent Prog Horm Res 57: 257–275

Cabanac M, Massonnet B (1977) Thermoregulatory responses as a function of core temperature in humans. J Physiol 265: 587–596

Charkoudian N (2003) Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. Mayo Clin Proc 78: 603–612

Clayden JR (1972) Effect of clonidine on menopausal flushing. Lancet ii: 1361

Clayden JR, Bell JW, Pollard P (1974) Menopausal flushing: double-blind trial of a non-hormonal medication. Br Med J i: 409–412

Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL (2006) Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 63: 385–390

Crawshaw L, Grahn D, Wollmuth L, Simpson L (1985) Central nervous regulation of body temperature in vertebrates: comparative aspects. Pharmacol Ther 30: 19–30

Crompton MR (1971) Hypothalamic lesions following closed head injury. Brain 94: 165–172

Deecher DC (2005) Physiology of thermoregulatory dysfunction and current approaches to the treatment of vasomotor symptoms. Expert Opin Investig Drugs 14: 435–448

Deecher DC, Alfinito PD, Leventhal L, Cosmi S, Johnston GH, Merchenthaler I, Winneker R (2007) Alleviation of thermoregulatory dysfunction with the new serotonin and norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized rodent models. Endocrinology 148: 1376–1383

Dennerstein L, Smith AM, Morse CA, Burger HG (1994) Sexuality and the menopause. J Psychosom Obstet Gynaecol 15: 59–66

Dugan SA, Powell LH, Kravitz HM, Everson Rose SA, Karavolos K, Luborsky J (2006) Musculoskeletal pain and menopausal tatus. Clin J Pain 22: 325–331

Edwards S, Lennox G, Robson K, Whiteley A (1996) Hypothermia due to hypothalamic involvement in multiple sclerosis. J Neurol Neurosurg Psychiatry 61: 419–420

Etgen AM, Ansonoff MA, Quesada A (2001) Mechanisms of ovarian steroid regulation of norepinephrine receptor-mediated signal transduction in the hypothalamus: implications for female reproductive physiology. Horm Behav 40: 169–177

Frank SM, Raja SN, Bulcao CF, Goldstein DS (1999) Relative contribution of core and cutaneous temperatures to thermal comfort and autonomic responses in humans. J Appl Physiol 86: 1588–1593

Freedman RR (2001) Physiology of hot flashes. Am J Hum Biol 13: 453–464

Freedman RR (2005) Hot flashes: behavioral treatments, mechanisms, and relation to sleep. Am J Med 118 (Suppl 12B): 124–130

Freedman RR, Krell W (1999) Reduced thermoregulatory null zone in postmenopausal women with hot flashes. Am J Obstet Gynecol 181: 66–70

Freedman RR, Woodward S (1995) Altered shivering threshold in postmenopausal women with hot flashes. Menopause 2: 163–168

Freedman RR, Woodward S (1996) Core body temperature during menopausal hot flushes. Fertil Steril 65: 1141–1144

Freedman RR, Norton D, Woodward S, Cornélissen G (1995) Core body temperature and circadian rhythm of hot flashes in menopausal women. J Clin Endocrinol Metab 80: 2354–2358

Freeman EW, Sammel MD, Lin H, Nelson DB (2006) Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry 63: 375–382

Genazzani AR, Lucchesi A, Stomati M, Catarsi S, Genazzani AD, Criscuolo M, Petraglia F (1997) Effects of sex steroid hormones on the neuroendocrine system. Eur J Contracept Reprod Health Care 2: 63–69

Genazzani AR, Pluchino N, Luisi S, Luisi M (2007) Estrogen, cognition and female ageing. Hum Reprod Update 13: 175–187

Gibbs RB (1998) Levels of trkA and BDNF mRNA, but not NGF mRNA, fluctuate across the estrous cycle and increase in response to acute hormone replacement. Brain Res 787: 259–268

Gould E, Woolley CS, Frankfurt M, McEwen BS (1990) Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. J Neurosci 10: 1286–1291

Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF (2007) Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol 109: 823–830

Gundlah C, Pecins-Thompson M, Schutzer WE, Bethea CL (1999) Ovarian steroid effects on serotonin 1A, 2A and 2C receptor mRNA in macaque hypothalamus. Brain Res Mol Brain Res 63: 325–339

Gundlah C, Kohama SG, Mirkes SJ, Garyfallou VT, Urbanski HF, Bethea CL (2000) Distribution of estrogen receptor beta (ERbeta) mRNA in hypothalamus, midbrain and temporal lobe of spayed macaque: continued expression with hormone replacement. Brain Res Mol Brain Res 76: 191–204

Gundlah C, Lu NZ, Bethea CL (2002) Ovarian steroid regulation of monoamine oxidase-A and -B mRNAs in the macaque dorsal raphe and hypothalamic nuclei. Psychopharmacology (Berl) 160: 271–282

Gundlah C, Alves SE, Clark JA, Pai LY, Schaeffer JM, Rohrer SP (2005) Estrogen receptor-beta regulates tryptophan hydroxylase-1 expression in the murine midbrain raphe. Biol Psychiatry 57: 938–942

Guthrie JR, Dennerstein L, Taffe JR, Lehert P, Burger HG (2004) The menopausal transition: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. Climacteric 7: 375–389

Guyton AC, Hall JE (2006) Textbook of medical physiology, 11th edn. Elsevier Saunders, Philadelphia, pp 889–901

Haimov-Kochman R, Barak-Glantz E, Arbel R, Leefsma M, Brzezinski A, Milwidsky A, Hochner-Celnikier D (2006) Gradual discontinuation of hormone therapy does not prevent the reappearance of climacteric symptoms: a randomized prospective study. Menopause 13: 370–376

Hendrix SL (2005) Bilateral oophorectomy and premature menopause. Am J Med 118 (Suppl 12B): 131–135

Hensel H (1973) Neural processes in thermoregulation. Physiol Rev 53: 948–1017

Herbison AE, Simonian SX, Thanky NR, Bicknell RJ (2000) Oestrogen modulation of noradrenaline neurotransmission. Novartis Found Symp 230: 74–85

Hiroi R, McDevitt RA, Neumaier JF (2006) Estrogen selectively increases tryptophan hydroxylase-2 mRNA expression in distinct subregions of rat midbrain raphe nucleus: association between gene expression and anxiety behavior in the open field. Biol Psychiatry 60: 288–295

Holzbeierlein JM, Castle EP, Thrasher JB (2003) Complications of androgen-deprivation therapy for prostate cancer. Clin Prostate Cancer 2: 147–152

Joffe H, Hall JE, Soares CN, Hennen J, Reilly CJ, Carlson K, Cohen LS (2002) Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. Menopause 9: 392–398

Jordan VC (2007) SERMs: meeting the promise of multifunctional medicines. J Natl Cancer Inst 99: 350–356

Joswig M, Hach-Wunderle V, Ziegler R, Nawroth PP (1999) Postmenopausal hormone replacement therapy and the vascular wall: mechanisms of 17 beta-estradiols effects' on vascular biology. Exp Clin Endocrinol Diabetes 107: 477–487

Kalló I, Liposits Z, Flerkó B, Coen CW (1992) Immunocytochemical characterization of afferents to estrogen receptor-containing neurons in the medial preoptic area of the rat. Neuroscience 50: 299–308

Karkanias GB, Etgen AM (1994) Estradiol reduction of the agonist high affinity form of the alpha 2-adrenoceptor in the hypothalamus of

female rats: identification as the alpha 2D subtype. Mol Pharmacol 45: 509–516
Karkanias GB, Ansonoff MA, Etgen AM (1996) Estradiol regulation of alpha 1b-adrenoceptor mRNA in female rat hypothalamus-preoptic area. J Neuroendocrinol 8: 449–455
Karkanias GB, Li CS, Etgen AM (1997) Estradiol reduction of alpha 2-adrenoceptor binding in female rat cortex is correlated with decreases in alpha 2A/D-adrenoceptor messenger RNA. Neuroscience 81: 593–597
Kronenberg F (1990) Hot flashes: epidemiology and physiology. Ann NY Acad Sci 592: 52–86
Kronenberg F (1999) Hot flashes. In: Lobo RA (ed) Treatment of the postmenopausal woman: basic and clinical aspects, 2nd edn. Lippincott Williams & Wilkins, Philadelphia, pp 157–177
Kurz A, Sessler DI, Tayefeh F, Goldberger R (1998) Poikilothermia syndrome. J Intern Med 244: 431–436
Land SR, Wickerham DL, Costantino JP, Ritter MW, Vogel VG, Lee M, Pajon ER, Wade JL III, Dakhil S, Lockhart JB Jr, Wolmark N, Ganz PA (2006) Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA 295: 2742–2751
Le Saux M, Di Paolo T (2005) Changes in 5-HT1A receptor binding and G-protein activation in the rat brain after estrogen treatment: comparison with tamoxifen and raloxifene. J Psychiatry Neurosci 30: 110–117
Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, Novotny PJ, Dakhil SR, Rodger K, Rummans TA, Christensen BJ (2000) Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 356: 2059–2063
Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, Halyard MY, Pruthi S, Novotny PJ, Rummans TA (2002) Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 20: 1578–1583
Lu H, Ozawa H, Nishi M, Ito T, Kawata M (2001) Serotonergic neurones in the dorsal raphe nucleus that project into the medial preoptic area contain oestrogen receptor beta. J Neuroendocrinol 13: 839–845
Lu NZ, Bethea CL (2002) Ovarian steroid regulation of 5-HT1A receptor binding and G protein activation in female monkeys. Neuropsychopharmacology 27: 12–24
Martin GR (1994) Vascular receptors for 5-hydroxytryptamine: distribution, function and classification. Pharmacol Ther 62: 283–324
Maswood N, Cosmi S, Alfinito PD, Leventhal L, Deecher DC (2006) The role of the selective serotonin reuptake inhibitor fluoxetine in temperature regulation in ovariectomized rat models. Neuroendocrinology 84: 330–338
McEwen B (2002) Estrogen actions throughout the brain. Recent Prog Horm Res 57: 357–384
McEwen BS (2001) Invited review: estrogens effects on the brain: multiple sites and molecular mechanisms. J Appl Physiol 91: 2785–2801
McEwen BS, Alves SE (1999) Estrogen actions in the central nervous system. Endocr Rev 20: 279–307
Mom CH, Buijs C, Willemse PH, Mourits MJ, de Vries EG (2006) Hot flushes in breast cancer patients. Crit Rev Oncol Hematol 57: 63–77
National Institutes of Health (2005a) National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med 142: 1003–1013
National Institutes of Health (2005b) NIH State-of-the-Science Conference Statement on management of menopause-related symptoms. NIH Consensus Development Program; 2005. Available at http://consensus.nih.gov/2005/2005MenopausalSymptomsSOS025html.htm. Accessed 27 September 2007
Nelson HD, Haney E, Humphrey L, Miller J, Nedrow A, Nicolaidis C, Vesco K, Walker M, Bougatsos C, Nygren P (2005) Management of menopause-related symptoms. Evid Rep Technol Assess (Summ) 120: 1–6
Nelson HD, Vesco KK, Haney E (2006a) Clonidine, gabapentin, and some SSRIs effective for hot flashes. J Fam Pract 55: 662
Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L (2006b) Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA 295: 2057–2071
Ness J, Aronow WS, Beck G (2006) Menopausal symptoms after cessation of hormone replacement therapy. Maturitas 53: 356–361
North American Menopause Society (2004a) Treatment of menopause-associated vasomotor symptoms: position statement of The North American Menopause Society. Menopause 11: 11–33
North American Menopause Society (2004b) Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of The North American Menopause Society. Menopause 11: 589–600
Osterlund MK, Gustafsson JA, Keller E, Hurd YL (2000) Estrogen receptor beta (ERbeta) messenger ribonucleic acid (mRNA) expression within the human forebrain: distinct distribution pattern to ERalpha mRNA. J Clin Endocrinol Metab 85: 3840–3846
Øverlie I, Moen MH, Holte A, Finset A (2002) Androgens and estrogens in relation to hot flushes during the menopausal transition. Maturitas 41: 69–77
Pecins-Thompson M, Brown NA, Kohama SG, Bethea CL (1996) Ovarian steroid regulation of tryptophan hydroxylase mRNA expression in rhesus macaques. J Neurosci 16: 7021–7029
Petitti N, Etgen AM (1990) Alpha 1-adrenoceptor augmentation of beta-stimulated cAMP formation is enhanced by estrogen and reduced by progesterone in rat hypothalamic slices. J Neurosci 10: 2842–2849
Randolph JF Jr, Sowers M, Bondarenko I, Gold EB, Greendale GA, Bromberger JT, Brockwell SE, Matthews KA (2005) The relationship of longitudinal change in reproductive hormones and vasomotor symptoms during the menopausal transition. J Clin Endocrinol Metab 90: 6106–6112
Rödström K, Bengtsson C, Lissner L, Milsom I, Sundh V, Bjorkelund C (2002) A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. Menopause 9: 156–161
Romanovsky AA (2007) Thermoregulation: some concepts have changed. Functional architecture of the thermoregulatory system. Am J Physiol Regul Integr Comp Physiol 292: R37–R46
Sanchez RL, Reddy AP, Centeno ML, Henderson JA, Bethea CL (2005) A second tryptophan hydroxylase isoform, TPH-2 mRNA, is increased by ovarian steroids in the raphe region of macaques. Brain Res Mol Brain Res 135: 194–203
Santoro N (2005) The menopausal transition. Am J Med 118 (Suppl 12B): 8–13
Santoro N, Brown JR, Adel T, Skurnick JH (1996) Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 81: 1495–1501
Serova L, Rivkin M, Nakashima A, Sabban EL (2002) Estradiol stimulates gene expression of norepinephrine biosynthetic enzymes in rat locus coeruleus. Neuroendocrinology 75: 193–200
Serova LI, Maharjan S, Huang A, Sun D, Kaley G, Sabban EL (2004) Response of tyrosine hydroxylase and GTP cyclohydrolase I gene expression to estrogen in brain catecholaminergic regions varies with mode of administration. Brain Res 1015: 1–8
Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL (2002) Pathophysiology and treatment of hot flashes. Mayo Clin Proc 77: 1207–1218
Shaver JL, Paulsen VM (1993) Sleep, psychological distress, and somatic symptoms in perimenopausal women. Fam Pract Res J 13: 373–384
Simon E (2000) The enigma of deep-body thermosensory specificity. Int J Biometeorol 44: 105–120

Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N (2001) Executive summary: stages of reproductive aging workshop (STRAW). Fertil Steril 76: 874–878

Stearns V, Beebe KL, Iyengar M, Dube E (2003) Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 289: 2827–2834

Stearns V, Slack R, Greep N, Henry-Tilman R, Osborne M, Bunnell C, Ullmer L, Gallagher A, Cullen J, Gehan E, Hayes DF, Isaacs C (2005) Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol 23: 6919–6930

Sullivan F, Hutchinson M, Bahandeka S, Moore RE (1987) Chronic hypothermia in multiple sclerosis. J Neurol Neurosurg Psychiatry 50: 813–815

Suvanto-Luukkonen E, Koivunen R, Sundstrom H, Bloigu R, Karjalainen E, Haiva-Mallinen L, Tapanainen JS (2005) Citalopram and fluoxetine in the treatment of postmenopausal symptoms: a prospective, randomized, 9-month, placebo-controlled, double-blind study. Menopause 12: 18–26

Tataryn IV, Lomax P, Bajorek JG, Chesarek W, Meldrum DR, Judd HL (1980) Postmenopausal hot flushes: a disorder of thermoregulation. Maturitas 2: 101–107

Temel S, Lin W, Lakhlani S, Jennes L (2002) Expression of estrogen receptor-alpha and cFos in norepinephrine and epinephrine neurons of young and middle-aged rats during the steroid-induced luteinizing hormone surge. Endocrinology 143: 3974–3983

Thompson HJ, Tkacs NC, Saatman KE, Raghupathi R, McIntosh TK (2003) Hyperthermia following traumatic brain injury: a critical evaluation. Neurobiol Dis 12: 163–173

Utian WH (2005) Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Health Qual Life Outcomes 3: 47–56

Williams CW (1973) Clonidine in treatment of menopausal flushing. Lancet i: 1388

White KD, Scoones DJ, Newman PK (1996) Hypothermia in multiple sclerosis. J Neurol Neurosurg Psychiatry 61: 369–375

Woodward S, Freedman RR (1994) The thermoregulatory effects of menopausal hot flashes on sleep. Sleep 17: 497–501

Woolley CS, McEwen BS (1993) Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. J Comp Neurol 336: 293–306

Zhang YH, Yamada K, Hosono T, Chen XM, Shiosaka S, Kanosue K (1997) Efferent neuronal organization of thermoregulatory vasomotor control. Ann N Y Acad Sci 813: 117–122