WHITE PAPER

VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE: NEW AND EMERGING EVIDENCE ON NEURAL MECHANISMS

This white paper is intended to provide an overview of selected topics related to the new and emerging evidence underlying the mechanisms of vasomotor symptoms associated with menopause (VMS). This information is not intended to serve as a substitute for sound clinical judgment or decision making, and professional experience. The content or material provided herein is for informational purposes only and should not be construed as medical or other professional advice or opinion. Information herein is not intended for the diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease.

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EXPLORING THE SCIENCE BEHIND VMS

FACULTY

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Risa Kagan, MD, FACOG, NCMP
Clinical Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California at San Francisco, Sutter East Bay Medical Foundation
Berkeley, CA

Ekta Kapoor, MBBS
Consultant, Division of General Internal Medicine and Division of Endocrinology, Diabetes, Metabolism, and Nutrition; Department of Medicine, Mayo Clinic
Associate Professor of Medicine
Mayo Clinic College of Medicine and Science
Assistant Director, Mayo Clinic Center for Women's Health, Rochester, MN

Richard Payne, MD
Fellow, American Board of Family Medicine
North Coast Family Medical Group
Clinical Instructor, Department of Family Medicine
University of California, San Diego School of Medicine
Chair, Physician Health and Well Being Committee, Scripps Memorial Hospital
Encinitas, CA

Pauline Maki, PhD
Professor, Departments of Psychiatry and Psychology
Professor, Department of Obstetrics & Gynecology
Director, Women's Mental Health Research
Senior Director of Research, UIC Center for Research on Women & Gender
University of Illinois at Chicago, Chicago, IL

Gloria Richard-Davis, MD, MBA, NCMP, FACOG
Executive Director, Division of Diversity, Equity & Inclusion
Professor, Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
University of Arkansas Medical Sciences, Little Rock, AR

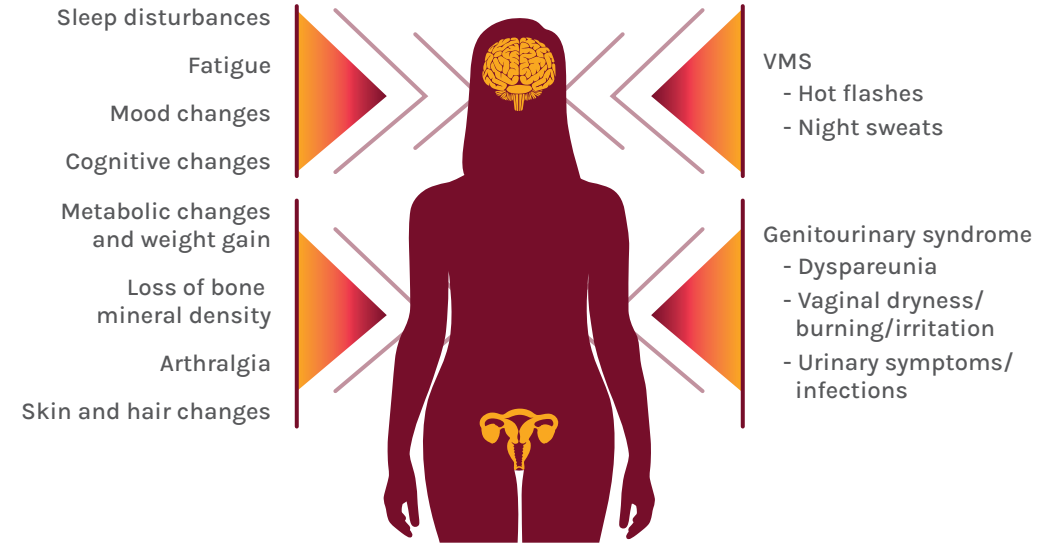
INTRODUCTION

Hot flashes and night sweats, also known as vasomotor symptoms, are the hallmark symptoms of menopause.[1] While the precise mechanisms are unknown, a growing body of literature has provided new evidence that a population of neurons in the hypothalamus, a part of the brain that regulates body temperature, may mediate vasomotor symptoms associated with menopause (VMS).[1,2] In this white paper, we review key findings from several different avenues of research that have helped to advance our understanding of how VMS are mediated during menopause.

VMS: PREVALENCE, DURATION, AND IMPACT

Natural menopause is a normal physiologic event defined as the permanent cessation of menses due to loss of ovarian follicular activity.[3] It is determined retrospectively after 12 consecutive months of amenorrhea after the final menstrual period (FMP). Menopause usually occurs between 40 and 58 years of age.[3] Onset before age 45 is considered early menopause, after age 54 is considered late menopause, and prior to age 40 is known as premature menopause or primary ovarian insufficiency.[3] Women who are undergoing natural menopause experience benchmark phases known as perimenopause and postmenopause.[3,4] Perimenopause, the years of transition from the reproductive period to 1 year after the FMP, is characterized by changes in bleeding patterns, marked fluctuations in reproductive hormone levels, and a high symptom burden.[3,4] Menopausal symptoms and conditions include VMS, genitourinary syndrome, metabolic changes and weight gain, loss of bone mineral density, sleep disturbances, depression and anxiety, cognitive changes, and skin and hair changes (**Figure 1**).[5,6] The occurrence and severity of menopausal symptoms women experience can vary widely and are influenced by multiple variables including race, ethnicity, comorbidities, lifestyle factors, and psychosocial factors.[5,7]

Figure 1. Menopausal signs and symptoms[1,5,6]



VMS are commonly known as hot flashes and night sweats.[1,8]

Hot flashes: *Episodes of sudden intense sensation of heat in the upper body lasting 1 to 5 minutes; may be accompanied by sweating, chills, anxiety, and heart palpitations[8]*

Night sweats: *Hot flashes that occur during sleep[1]*

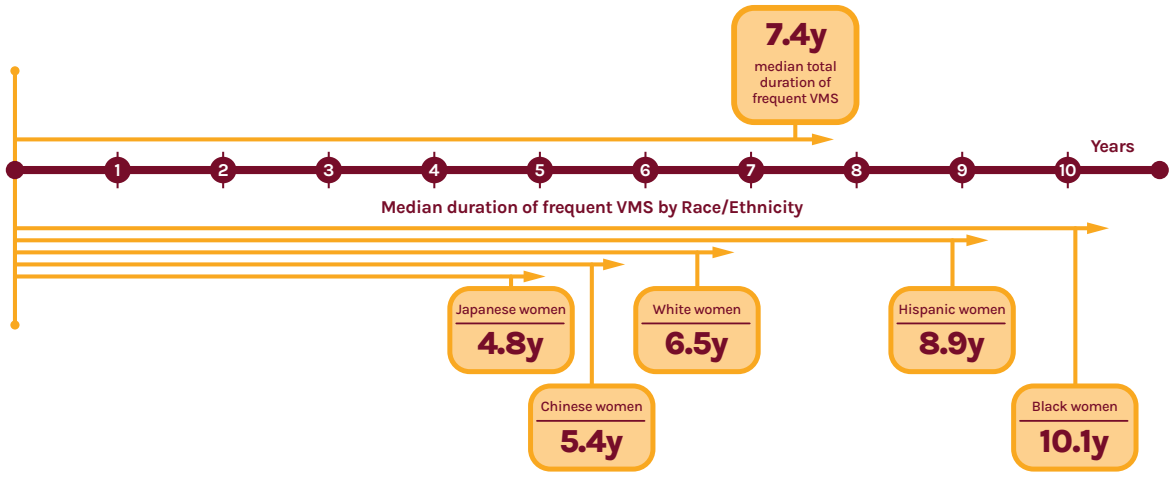
VMS are a heat dissipation response involving widespread cutaneous vasodilation which increases skin temperature and may be accompanied by profuse upper body sweating.[1,9] Vasodilatation and sweating are heat dissipation effectors activated during hot flashes.[2] A small increase in core temperature is seen before the hot flash, followed by a larger drop due to the activation of heat dissipation effectors.[2]

Vasomotor symptoms, characterized by hot flashes and/or night sweats, are the most common and bothersome symptoms reported during menopause and are a chief complaint among women who are seeking care for their menopausal symptoms.[1,5,12] Up to 80% of women in the United States experience VMS at some point during the menopausal transition.[13] The proportion of women experiencing moderate to severe VMS varies.[14] In a global survey, the prevalence of moderate to severe VMS was greatest in women from European countries (40%), followed by the United States (34%) and Japan (16%).[14] The frequency with which women experience VMS also varies. In a United States survey of perimenopausal and postmenopausal women, nearly a quarter experienced hot flashes every day and the daily frequency of hot flashes ranged from 1-2 per day (63%) to 7 or more per day (6%).[15] In a UK study of older postmenopausal women, aged between 54 and 65 years, over half reported they were continuing to experience VMS, averaging 33 episodes per week.[16]

Women may experience VMS beginning as early as the premenopausal years through late postmenopause.[17,18] The occurrence of VMS varies, but generally peaks within the first 2 years of the FMP.[10,11,17] Women can experience VMS for many years—the median duration of VMS among women who report frequent VMS is 7.4 years; some women experience moderate to severe VMS for 10 years or more (**Figure 2**).[19,20] Moderate to severe VMS have been shown to be highly prevalent in postmenopausal women who are in their 60s.[21] VMS disproportionately affect women from different racial and ethnic groups.[19] In the United States, the prevalence of VMS are greatest among African American (46%) and Hispanic (35%) women, followed by Caucasian (31%), Chinese (21%) and Japanese (18%) women.[22] The median duration of VMS is 10.1 years in African American women, 8.9 years for Hispanic women, 6.5 years for white women, 5.4 years in Chinese women, and 4.8 years in Japanese women (**Figure 2**).[19]

60% to 80% of women will experience VMS at some point as they are transitioning through menopause, and nearly half may experience moderate to severe symptoms.[1,10,11]

Figure 2. Overall, the median total duration of VMS is 7.4 years. However, the duration of VMS varies by race/ethnicity and some women may experience symptoms for 10 or more years[19a]



[a]Analysis of 1449 women with frequent VMS enrolled in SWAN. This was a prospective, community-based, multiracial/multiethnic, longitudinal cohort study of 3302 women enrolled at 7 US sites. Frequent VMS was defined as hot flashes or night sweats occurring ≥6 days in the prior 2 weeks.

SWAN, Study of Women's Health Across the Nation; y, years.

VMS have a negative impact on many aspects of women's lives and society:[1,23–28]

- ***Sleep disruption***
- ***Mood disturbances***
- ***Cognitive function***
- ***Social isolation***
- ***Loss of work productivity***
- ***Increased healthcare cost and utilization of resources***

VMS may be a marker for future chronic disease[1,29,30]

- ***Risk of cardiovascular disease***
- ***Poor bone health***

Hot flashes and night sweats can have a negative impact on women's quality of life and well-being, including sleep disruption, depressed mood, anxiety, cognitive function, and social embarrassment/isolation.[1,24–26] In addition, VMS can cause loss of work productivity and increased healthcare costs and utilization.[27,28] Studies have also shown that the frequency and severity of VMS may be a marker for future chronic disease, such as cardiovascular disease and poor bone health.[1,29,30]

Hot flashes and night sweats are considered the most bothersome symptoms associated with menopause and a common reason women seek medical care.[12,31] Yet, more than 70% of women with moderate to severe VMS may go untreated.[27]

Treatment options for VMS include hormone therapy (HT), nonhormonal pharmacologic therapy, and other therapies such as mind–body techniques, lifestyle changes, and dietary supplements.[32,33] Hormone therapy is recognized as the gold standard for the treatment of VMS.[32] According to the 2017 HT position statement of the North American Menopause Society, HT is an appropriate option for bothersome VMS "for women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications".[32] Yet, many women choose not to use HT.[34,35] There is only one nonhormonal pharmacologic therapy, a selective serotonin reuptake inhibitor (SSRI), that is approved by the United States Food and Drug Administration for the treatment of moderate to severe VMS.[33] Other nonhormonal pharmacologic therapies have been investigated, however, their efficacy and side-effect profile have limited their use for the treatment of VMS.[33] Two mind–body techniques—cognitive behavior therapy and hypnosis—have been found to be effective in reducing VMS.[33] The efficacy of lifestyle changes (ie, yoga, exercise, cooling techniques), dietary supplements, herbal remedies, and other therapies (ie, acupuncture, stellate ganglion block, or chiropractic intervention) are less studied, but generally have not been shown to reduce VMS.[33] Given the impact and disruption to women's lives, there is an unmet need for improved management of hot flashes and night sweats.

NEUROENDOCRINE CHANGES IN MENOPAUSE

The clinical manifestations of menopause arise from neuroendocrine changes in the reproductive axis that govern ovarian function.[5] During the transition into menopause, the hypothalamic-pituitary-ovarian (HPO) axis undergoes a series of changes that are driven by the depletion of ovarian follicles.[3] The loss of ovarian follicles leads to a decrease in circulating estrogen and consequently a loss of estrogen-negative feedback on the hypothalamus and the pituitary gland (**Figure 3**).[2] With the loss of estrogen, there is an increase in the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, and a subsequent increase in the release of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), from the pituitary.[2]

Our understanding of the neuroendocrine signals that control the reproductive axis was revolutionized when researchers identified a population of neurons located in the hypothalamus that play a critical role in the control of GnRH release.[36] These neurons contain the neuropeptides kisspeptin, neurokinin B (NKB), and dynorphin, and are known as KNDy neurons.[36]

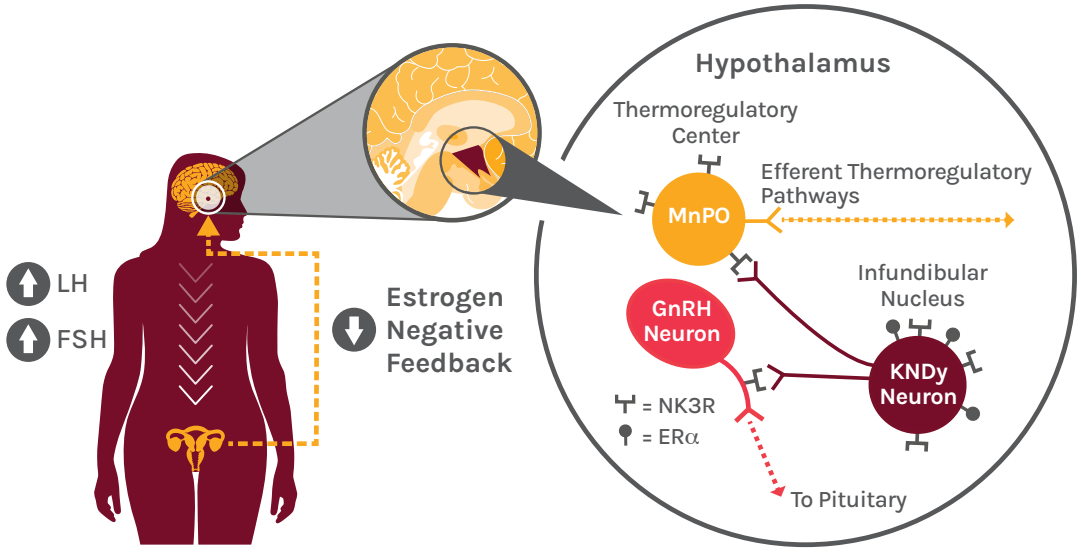
Further, these neurons have estrogen receptors, making them sensitive to feedback from estrogen.[2,36] The estrogen-sensitive KNDy neurons synapse on the GnRH-containing neurons in the hypothalamus and, therefore, have an important role in relaying feedback to control GnRH release and subsequently release of LH and FSH from the pituitary (**Figure 3**).[36,37] Interestingly, the KNDy neurons also project to other regions of the hypothalamus, including a region that is involved in thermoregulation.[38] We will discuss below the growing body of evidence that shows how this pathway in the brain is involved in mediating VMS.

KNDy neurons are estrogen-sensitive neurons in the hypothalamus that contain the neuropeptides kisspeptin, neurokinin B (NKB), and dynorphin.[36]

PATHOPHYSIOLOGY OF VMS

Our understanding of the etiology of VMS has continued to evolve. Over the years, multiple mechanisms have been carefully studied.[1] Declining ovarian estrogen is thought to be important to the pathophysiology of VMS, yet there is only a modest correlation between VMS and circulating estrogen levels.[1] Overall, the evidence suggests that VMS likely represent a complex interplay between multiple central and peripheral physiologic processes.[1] In addition to declines in estrogen, some of the mechanisms that have been studied include thermoregulatory models whereby narrowing of the thermoneutral zone in menopausal women and small changes in body temperature trigger a hot flash, dysregulation of the autonomic nervous system control of vasoconstriction and cardiac function, the central adrenergic nervous system, serotonergic mechanisms, and other processes affecting the hypothalamic-pituitary-adrenal axis, endothelial cell dysfunction, and proinflammatory mechanisms.[1,9]

Figure 3. Changes in the HPO axis during the menopausal transition and the relationship of KNDy neurons, GnRH neurons, and the thermoregulatory center in the hypothalamus[2]



Left: In the menopausal transition, there is a loss of ovarian follicles, a decrease in estrogen released from the ovaries, and a subsequent decrease in estrogen-negative feedback on the pituitary and the hypothalamus. Loss of estrogen-negative feedback results in an increase in LH and FSH secretion.[2,3,5]

Right: Estrogen-sensitive KNDy neurons in the hypothalamus project to both GnRH-containing neurons to control pulsatile GnRH release and to neurons in a region of hypothalamus involved in regulating body temperature (the MnPO). Efferent thermoregulatory pathways from the MnPO modulate heat dissipation effectors (vasodilation and sweating).[2,36,37]

ERα, estrogen receptor alpha; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HPO; hypothalamic-pituitary-ovarian; KNDy, kisspeptin-neurokinin B-dynorphin; LH, luteinizing hormone; MnPO, median preoptic nucleus; NK3R, neurokinin 3 receptor.

Hypertrophy of KNDy neurons in the hypothalamus has been observed in postmortem brain tissue of postmenopausal but not premenopausal women.[2]

Early on, studies found that there is close timing between pulses of LH and hot flashes in menopausal women.[39] This was an important clue that the mechanisms underlying menopausal hot flashes could be related to the mechanisms in the hypothalamus that control GnRH release.[2] Rance and colleagues identified a subset of estrogen receptor bearing neurons in the infundibular nucleus of the hypothalamus that undergo hypertrophy in postmenopausal women but not in premenopausal women.[40] Furthermore, these investigators observed an increase in the number of neurons expressing kisspeptin mRNA and NKB mRNA in the hypothalamus of postmenopausal women but not in premenopausal women (**Figure 4**).[41,42] Interestingly, this is the same region of the hypothalamus where the subpopulation of estrogen-sensitive KNDy neurons described above were found to be important in mediating pulsatile GnRH release.[36,37] The dramatic changes observed in the KNDy neurons in the infundibular nucleus of the hypothalamus in postmenopausal women suggested that these neurons might be involved in mediating VMS.[2] These early observations and subsequent research from several groups have greatly expanded our understanding of the role of the KNDy neurons in thermoregulation and in VMS. The culmination of this extensive body of research has led to the mechanisms described below.

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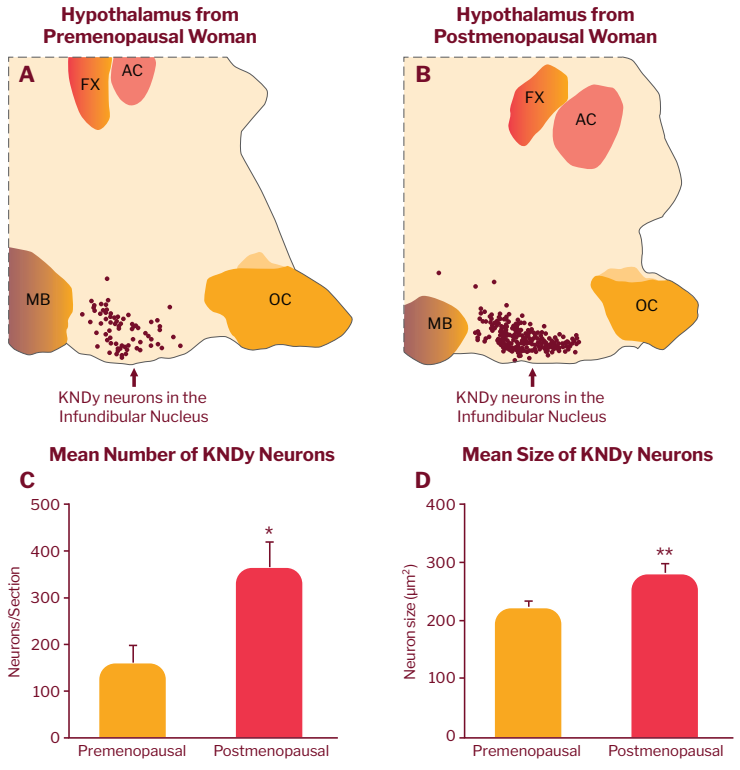
Figure 4. Hypertrophy of KNDy neurons in the hypothalamus was observed in postmenopausal but not premenopausal women[2,41,42]



Illustrations depict an increase in the number of neurons in the infundibular nucleus that express kisspeptin mRNA in postmortem brain sections of the hypothalamus taken from a premenopausal **(A)** and a postmenopausal **(B)** woman. The average number of neurons that express kisspeptin mRNA **(C)** and the size **(D)** of these neurons in the hypothalamus was greater in postmenopausal women compared with premenopausal women.[42]

To identify the kisspeptin mRNA, the investigators used probes that bind to the mRNA. Each symbol represents one neuron labeled with the kisspeptin mRNA probe.[42]

Nearly identical changes were seen in the increased expression of neurokinin B mRNA in the neurons in the infundibular nucleus of postmenopausal women.[2]

Probes for kisspeptin and neurokinin B mRNA were used to identify and label the KNDy neurons.[41,42]

AC, anterior commissure; FX, fornix; KNDy, kisspeptin/neurokinin B/dynorphin; MB, mammillary body; OC, optic chiasm.

*significantly different from premenopausal women ($p<0.001$).[42]
**significantly different from premenopausal women ($p<0.05$).[42]

Adapted from Rometo AM, et al. 2007.

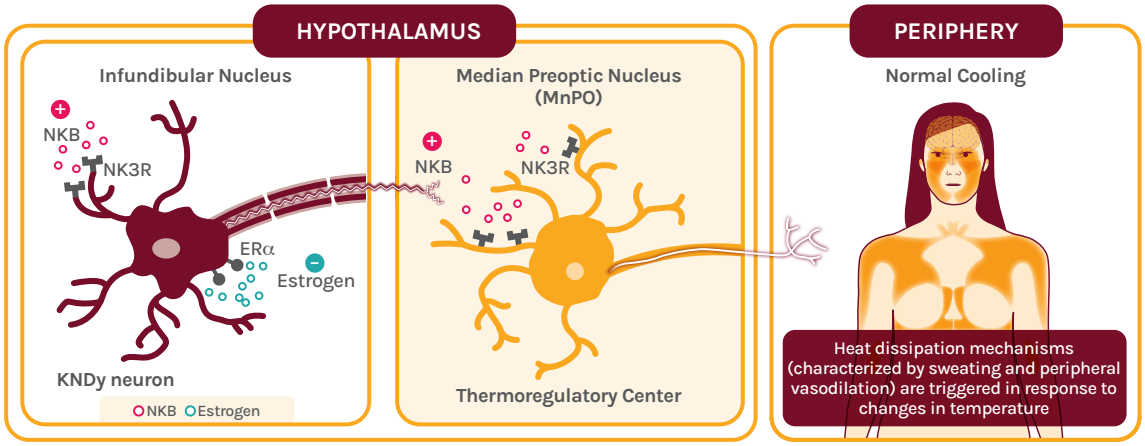
Investigators have shown that the KNDy neurons in the hypothalamus bearing NK3 receptors could be the link between estrogen decline and hot flashes.[2]

Through a series of pioneering studies conducted in humans and in animals, investigators suggested that KNDy neurons in the hypothalamus are the link between estrogen decline and hot flashes (**Figure 3**).[2] Administration of an NKB infusion that activates its receptors, known as neurokinin 3 (NK3) receptors, rapidly induced hot flash symptoms in premenopausal women, including increased heart rate and skin temperature changes.[43] Animal models have been used to study the role of KNDy neurons in hot flashes. In animals, removal of the ovaries (ovariectomy) simulates the decline in estrogen that is observed in menopause.[2] Vasodilation of the tail skin, a heat dissipation effector, can be monitored via changes in tail skin temperature and serves as a rodent model of hot flashes.[2] In these rodent models, ovariectomy resulted in an increase in tail skin temperature that was reversed with estrogen administration.[44] Also in rodents, ablating the KNDy neurons in the hypothalamus reduced tail skin temperature and the responsiveness to estrogen, suggesting that these neurons are critical in mediating the hot flash–like symptoms in this animal model.[45] Investigators mapped regions of the brain where the KNDy neurons project and, as noted above, found that these neurons also project to a region of the hypothalamus that is involved in thermoregulation.[2,38] As shown in **Figure 3**, the KNDy neurons in the hypothalamus send projections both to the hypothalamic GnRH neurons and to the median preoptic nucleus (MnPO), a region of the hypothalamus involved in thermoregulation.[2] The MnPO neurons also have receptors for NKB that are known as NK3 receptors; they receive information from skin thermoreceptors and project to other brain regions involved in temperature control.[2] Similar to studies in premenopausal women that found that infusion of NKB could modulate body temperature, investigators showed that microinfusion of a NK3 receptor agonist directly into the MnPO in rodents elicited a hot flash and subsequently reduced core body temperature.[43,46] In summary, these studies demonstrated that the KNDy neurons of the hypothalamus are important in relaying estrogen signals to brain pathways that regulate heat dissipation effectors, suggesting that these neurons play an important role in mediating menopausal hot flashes.[2]

Further evidence supporting a role of NKB in VMS has become available from research on genetic variation in its receptor. In a genome-wide analysis of women enrolled in the Women's Health Initiative Study (N=17,695), genetic variations known as single-nucleotide polymorphisms within the region of the *TACR3* gene, the gene that encodes the NK3 receptor, were associated with 1.4- to 1.6-fold higher odds of experiencing VMS.[47] This finding was consistent across women from the different ethnic groups.

Extensive research evaluating the potential role of KNDy neurons in mediating VMS has culminated in our understanding of the mechanisms depicted in **Figures 5A** and **5B.** Briefly, the KNDy neurons in the infundibular nucleus of the hypothalamus have estrogen receptors and receptors for NKB, NK3 receptors (**Figure 5A**).[45] Estrogen inhibits the activity of KNDy neurons and NKB stimulates these neurons.[45,46,48] The estrogen-sensitive KNDy neurons in the infundibular nucleus of the hypothalamus relay information to the thermoregulatory center in the hypothalamus, the MnPO.[1,46,48] When estrogen and NKB are counterbalanced, normal cooling occurs in response to increases in body temperature.[2] The thermoregulatory center initiates peripheral heat dissipation mechanisms, vasodilation and sweating.[2] When estrogen levels decline during menopause, activation of the KNDy neurons by NKB goes unopposed (**Figure 5B**).[45] When no longer counterbalanced by estrogen inhibition, NKB signaling can overstimulate the KNDy neurons in the infundibular region of the hypothalamus and these neurons become hypertrophied in menopause.[2] Increased activity of the KNDy neurons leads to altered signaling into the MnPO.[45,46,49] Increased activation of the MnPO neurons disrupts the thermoregulatory response, triggering activation of heat dissipation mechanisms experienced as VMS.[45,46]

Figure 5A. The thermoregulatory center of the hypothalamus is innervated by KNDy neurons that are stimulated by NKB and inhibited by estrogen[1,43,45,46,48]



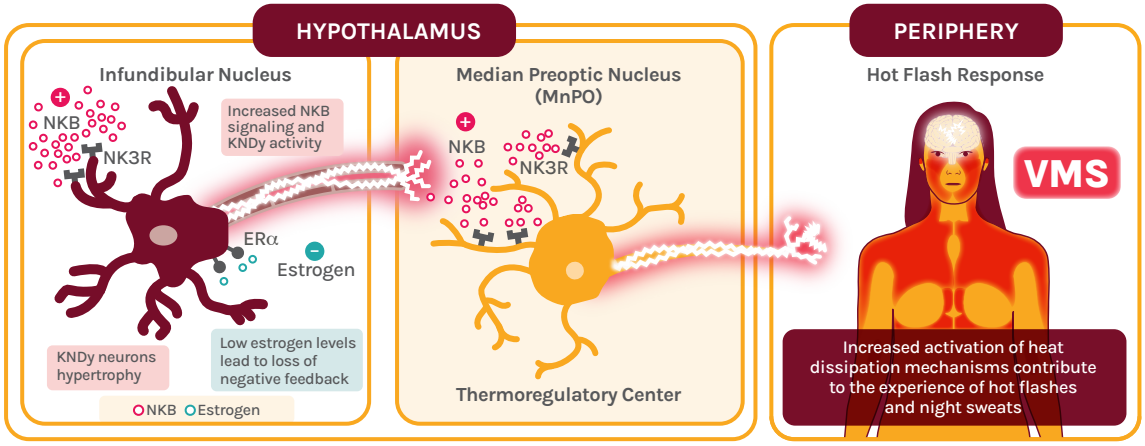
Panel 1: KNDy neurons of the infundibular nucleus of the hypothalamus are inhibited by estrogen and activated by NKB following binding to the NK3R.[45]

Panel 2: KNDy neurons project to the thermoregulatory center of the hypothalamus (the median preoptic nucleus) to modulate heat dissipation effectors.[1,38,45]

Panel 3: The normal cooling response to changes in temperature is to activate heat dissipation mechanisms (characterized by peripheral vasodilation and sweating).[2]

CNS, central nervous system; ERα, estrogen receptor alpha; KNDy, kisspeptin/neurokinin B/dynorphin; NKB, neurokinin B; NK3R, neurokinin 3 receptor.

Figure 5B. Declining estrogen levels during menopause leave NKB signaling unopposed and lead to altered signaling to the thermoregulatory center[2]



Panel 1: During menopause, the decline in estrogen leaves the NKB activation of the KNDy neurons of the infundibular nucleus of the hypothalamus unopposed. KNDy neurons become hypertrophied in menopause.[2,45]

Panel 2: There is increased signaling of KNDy neurons into the thermoregulatory center of the hypothalamus (the MnPO). Altered signaling in the MnPO disrupts the thermoregulatory response and activates heat dissipation mechanisms.[2,44–46,49]

Panel 3: Increased activation of the heat dissipation effectors (peripheral vasodilation and sweating) contributes to the experience of hot flashes and night sweats.[5]

ERα, estrogen receptor alpha; KNDy, kisspeptin, neurokinin B, and dynorphin-expressing neuron; MnPO, median preoptic nucleus; NKB, neurokinin B; NK3R, neurokinin 3 receptor.

KEY POINTS

- Vasomotor symptoms associated with menopause (VMS), characterized by hot flashes and/or night sweats, are the most common and bothersome symptoms reported during perimenopause and after menopause, and may have a significant negative impact on quality of life and well-being.
- VMS are a heat dissipation response involving widespread cutaneous vasodilation which increases skin temperature and may be accompanied by profuse upper body sweating. Vasodilation and sweating are physiological heat dissipation effectors that are activated during hot flashes.
- VMS are a common reason women seek medical care, yet many go untreated. Treatment options include HT, nonhormonal pharmacologic therapy, and other therapies, such as lifestyle changes. Given the impact on women's lives, there is an unmet need for improved management of VMS.
- A subpopulation of estrogen-sensitive neurons in the hypothalamus are thought to be a GnRH pulse generator and also project to the thermoregulatory center in the hypothalamus, the MnPO. These neurons contain the neuropeptides kisspeptin, neurokinin B, and dynorphin, and are known as KNDy neurons.
- Studies conducted in humans and in animals have shown that KNDy neurons in the hypothalamus may be the link between estrogen decline and hot flashes during menopause.
- The KNDy neurons in the hypothalamus are hypertrophied in postmenopausal women.
- Infusion of NKB in premenopausal women induces hot flash–like symptoms.
- The KNDy neurons in the hypothalamus are inhibited by estrogen and stimulated by NKB via the NK3 receptor in a delicate balance.
- A decline in estrogen levels during the menopausal transition leaves NKB activation of the KNDy neurons in the hypothalamus unopposed. This leads to increased activation of the KNDy neurons and, in turn, altered signaling to neurons in the temperature control center of the hypothalamus.
- Increased activation of neurons in the temperature control center disrupts the thermoregulatory response, triggering activation of heat dissipation mechanisms (vasodilation and sweating) experienced as VMS.

KNDy neurons, estrogen-sensitive neurons containing the neuropeptides kisspeptin, NKB, and dynorphin, are located in the hypothalamus.[36] These neurons are thought to play a critical role in regulating both pulsatile GnRH release and body temperature via their projections to GnRH neurons and the thermoregulatory region of the hypothalamus, respectively.[36–38] The KNDy neurons in the hypothalamus may be the link between estrogen decline and hot flashes.[2,45]

For more information on VMS from Astellas, please scan the QR code or access the materials directly via vmsneuron.com.

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