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COMPREHENSIVE REVIEW

Effects of menopause on temperature regulation

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ABSTRACT

Changes in thermoregulation, notably the emergence of hot flashes, occur during the menopause transition in association with reproductive hormonal changes. Hot flashes constitute the most characteristic symptom of menopause (prevalence of 50–80%), and have a substantial negative effect on quality of life. Here, we review the endocrine changes associated with menopause and the thermoregulatory system and its sensitivity to female sex hormones. We then review current knowledge on the underlying neural mechanisms of hot flashes and how the reproductive and thermoregulatory systems interact in females. We consider the kisspeptin-neurokinin B-dynorphin (KNDy) neuron complex, which becomes hyperactive when estradiol levels decrease. KNDy neurons project from the arcuate nucleus to thermoregulatory areas within the hypothalamic preoptic area, where heat loss mechanisms are triggered, including cutaneous vasodilation and sweating – characteristics of the hot flash. We describe the physiology and measurement of hot flashes and discuss the mixed research findings about thresholds for sweating in symptomatic individuals. We consider the unique situation of hot flashes that arise during sleep, and discuss the relationships between the environment, exercise, and body mass index with hot flashes. We also discuss the unique situation of surgical menopause (with oophorectomy) and cancer therapy, conditions that are associated with frequent, severe, hot flashes. We then provide an overview of treatments of hot flashes, including hormone therapy and targeted neurokinin B-antagonists, recently developed to target the neural mechanism of hot flashes. Finally, we highlight gaps in knowledge about menopausal thermoregulation and hot flashes and suggest future directions for research.

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Introduction

The transition from the reproductive stage into post-menopause is marked by the diminution of the ovarian reserve, the end of menstrual cycles, and associated endocrine changes. During the reproductive stage, the female sex hormones oscillate across the menstrual cycle, mediating not only ovary and uterine function, but also physiological functioning more broadly, including body temperature. A biphasic rhythm of body temperature (T_{body}) is observed across ovulatory menstrual cycle, with higher temperature during the luteal phase than the follicular phase, in parallel with the progesterone rise after ovulation [1]. During the menopause transition, the hormone environment changes, and ovulatory menstrual cycles become less frequent and then cease. Vasomotor symptoms (hot flashes and night sweats), which are one of the most common symptoms of the menopause transition and post-menopause, are a thermoregulatory phenomenon, probably reflecting the interaction between the reproductive and thermoregulatory systems in the hypothalamus. While hot flashes have been considered by some to be "just a nuisance," it is increasingly recognized that hot flashes have a negative and prolonged impact on quality of life in the domains of health, sleep, work performance, and relationships [2–4].

Here, we present an overview of the effects of menopause on temperature regulation, specifically the emergence of hot flashes. We first review the

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changes that are associated with menopause in the hypothalamus and in endocrinology, as well as the thermoregulatory system and its sensitivity to female sex hormones. We then review current knowledge on the underlying neural mechanisms of hot flashes and how the female reproductive and thermoregulatory systems interact. We describe the physiology of hot flashes, and consider hot flashes in the context of sleep, exercise, and the environment, including the potential influence of climate change on thermoregulation and the severity of hot flashes in menopausal individuals. We consider the unique situation of surgical menopause (with oophorectomy) and cancer therapy, conditions that are associated with increased incidence and intensity of hot flashes. We then discuss treatments for hot flashes, including menopausal hormone therapy and targeted neurokinin B-antagonists. Finally, we identify gaps in knowledge about thermoregulation in the context of menopause and suggest future directions for research.

Methods

The electronic databases PubMed and Google Scholar were employed to identify clinical and experimental studies that have investigated the link between menopause and thermoregulation and have been published exclusively in English-language, peer-reviewed journals (excluding conference abstracts). To retrieve relevant articles, searches incorporated the words "menopause" and "thermoregulation" complemented by various search terms: hypothalamus, postmenopause, hot flashes, hot flushes, hormone therapy, vasomotor symptoms, estrogen, progesterone, temperature, KNDy neuron, kisspeptin, neurokinin B, dynorphin, sleep, metabolic rate, exercise, heating, heat, fever, cooling, cold, climate change, and wearable sensors. Our assessment of full-text manuscripts determined their relevance, and we cross-referenced the reference lists to identify additional pertinent studies.

Menopause

Menopause is defined as the cessation of menstrual cycles caused by the decline of ovarian function. It occurs spontaneously with age but can also be induced by surgery, chemotherapy, or pelvic radiation therapy. The natural transition to menopause occurs gradually and involves several endocrine organs, mainly the ovaries, the uterus, the hypothalamus, and the pituitary gland [5].

The age of natural menopause is partly influenced by genetics, as suggested by studies that have compared menopause age in twins and mother-daughter combinations [6]. However, a systematic review of genetic studies that have investigated specific loci associated with menopause age revealed very few consistent associations, emphasizing the need for polygenic investigations, as well as interactions between genes and the environment [7]. Ethnicity, race, and sociodemographic factors are important determinants of menopause age, and should be considered in studies of menopause [6,8]. The strongest external factor that is known to influence menopause age is smoking, which is consistently found to advance menopause (move the onset earlier) by one to two years [6,9]. Higher socioeconomic status, use of hormonal contraceptives, and higher number of pregnancies have also been consistently associated with later menopausal age; however, there is less consistency among studies linking menopause age to other modifiable factors, including occupational factors (stress, night-shift, heavy-lifting), diet, physical activity, and sleep [6,10,11].

From a clinical and research perspective, it is important to use consistent nomenclature about the menopause transition. In 2001 the Stages of Reproductive Aging Workshop (STRAW) developed the STRAW criteria, a set of guidelines to classify the reproductive stages of individuals. In 2011, those criteria were updated (STRAW +10) to address limitations and to incorporate scientific advances in the field [12]. The last version is considered applicable regardless of an individual's age, ethnicity, anthropometry, or life context. The STRAW + 10 criteria include the regularity of the menstrual cycle as a key criterion, with endocrine levels of follicle stimulating hormone (FSH), anti-Müllerian hormone (AMH), inhibin B, as well as the antral follicle count (that is measurable via ovarian ultrasound), as supportive criteria (Figure 1) [12]. The early menopausal transition is marked by a persistent

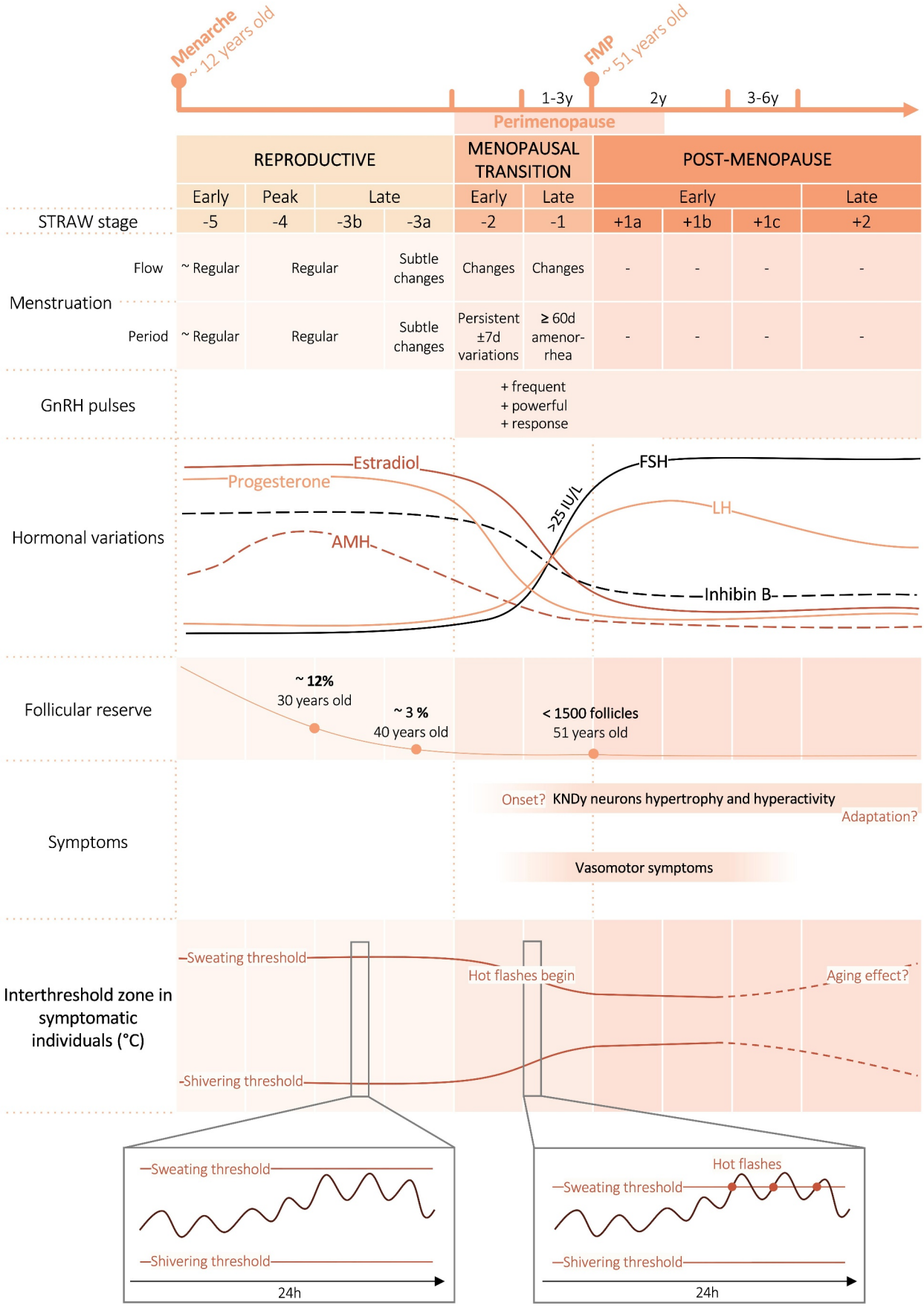

Figure 1. Summary of the STRAW criteria [12] showing the reproductive, menopausal transition, and post-menopause stages. The final menstrual period is retrospectively defined after 12 months without periods. Schematic representations of the changes reported

difference of seven days or more in the length of consecutive menstrual cycles, while the late menopausal transition is marked by amenorrhea of ≥60 days, increased variability in cycle length compared to the reproductive stage, and FSH levels ≥ 25 IU/l [12]. Menopause is declared retrospectively after 12 months without menses, following the final menstrual period. Early postmenopause describes the first two years after menopause, with increasing levels of FSH and decreasing levels of estradiol and progesterone, until hormone levels stabilize (Figure 1) [12]. Hormonal changes roughly map onto the STRAW stages, however, changes over time are non-linear [27] and ovulatory menstrual cycles can still occur during the menopausal transition [28], contributing to variability between individuals in hormonal patterns across the menopause transition [2,29]. Perimenopause encompasses the menopausal transition and the first year after the final menstrual period.

Premature ovarian failure, also known as primary ovarian insufficiency or primary ovarian dysfunction, happens before 40 years of age in about 1% of females. Spontaneous early menopause occurs between the ages of 40 and 45 years in around 5% of females, and can result from autoimmune disorders, genetic causes, infections, inflammatory conditions, enzyme deficiencies, or metabolic syndromes [30]. Early menopause can also be induced by treatments and surgeries, in general related to cancer, cancer risk, or hormone reactive cancers. For example, the potential damage caused to ovaries by chemotherapy or radiotherapy can induce ovarian failure [31,32]. In individuals with amenorrhea or unreliable bleeding patterns, such as with endometrial ablation, hysterectomy, treatment of malignancy, or chronic illness, the endocrine markers of ovarian aging, such as a rise in FSH, are required to identify the timing of the menopausal transition [33]. For those who have surgical menopause, including bilateral oophorectomy, menopause is rapidly induced, with a rise in FSH and drop in estradiol, and sudden appearance of menopausal symptoms, which are typically more severe than with natural menopause [34].

Definition, prevalence, and effects of hot flashes

A variety of symptoms are associated with the menopause transition, with important interindividual variability in the types and intensity of symptoms. Symptoms typically include vasomotor, genitourinary, psychological (depression and anxiety), libido, bone health, and sleep-related symptoms [15–17]. The vasomotor symptoms, which include hot flashes (also called hot flushes) and night sweats, are a thermoregulatory phenomenon. These terms are all used widely and often interchangeably in the literature. Vasomotor symptoms can be used as a scientific or clinical umbrella term because of the vascular reactivity that characterizes the events, with vasodilation followed by vasoconstriction [35]. Hot flashes typically last for one to five minutes [18] and can occur day or night [36]. According to self-reports, they typically originate at the face, neck, head or chest, and then spread outwards across the torso [37]. Some individuals have hot flashes hourly or daily, and others report only one or two hot flashes per week [36]. While the frequency of hot flashes varies between individuals it tends to remain consistent for an individual [38]. Night sweats is a term given to sweating episodes at night or hot flashes that occur at night; it is unclear whether hot flashes and night sweats differ mechanistically or physiologically, and individuals may interpret the terms differently when they are asked about their symptoms. In the literature, some refer to "hot flushes" and others, "hot flashes," partially dependent on country of origin. Voda (1981) differentiated "hot flush" from "hot flash," defining a flush as an observable change in skin color, which may or may not follow the spread of the hot flash from its point

in gonadotropin releasing hormone (GnRH) pulses [13], the reproductive endocrine system [13], and the follicular reserve [14] (middle panels). The two bottom panels highlight the hypothesized changes in KNDy neurons in the hypothalamus and narrowing of the inter-threshold zone that has been hypothesized to underlie the emergence of hot flashes across the stages of the menopausal transition and post-menopause, based on the combined work of [15–26] (although, see text for discussion about conflicting data about a narrowing of the inter-threshold zone).

of origin to other areas of the body [37]. However, Voda (1981) noted that not all hot flashes are followed or accompanied by a flush [37]. Here, we use the term "hot flashes."

Hot flashes constitute the most characteristic symptom of menopause with a high prevalence in people in most societies around the world [39]. In the USA, hot flashes occur in 50 to 82% of individuals who experience natural menopause, with significant variability by race and ethnicity, socioeconomic status, body mass, history of premenstrual syndrome, sedentary lifestyle, and smoking habits [,40]. The Study of Women Across the Nation (SWAN) found that African American women and those with a higher body mass index were more likely to report vasomotor symptoms and that those who identified as Japanese or Chinese were least likely to report vasomotor symptoms [41]. There is limited evidence for an underlying genetic contribution to the expression of hot flashes. However, Crandall and colleagues (2016), using data from three genome-wide association studies in racially/ethnically diverse populations of post-menopausal individuals in the USA (total $n = 17{,}695$), discovered 14 single nucleotide polymorphisms on chromosome 4 in the locus of tachykinin receptor 3 (TACR3) were associated with the risk of vasomotor symptoms, supporting a role for TACR3, which encodes the receptor for neurokinin B (NK_3R), in hot flashes [42].

In the USA, SWAN provided a longitudinal perspective from tracking monthly reports of hot flashes (yes/no) across the final menstrual period in a sample of 955 individuals [43]. Approximately 20% of individuals reported hot flashes five to eight years before their final menstrual period. The prevalence began increasing approximately four years before the last menstrual period, with about 48% reporting hot flashes in the final year before last menstrual period, followed by a sharp rise to ~ 60% during the year after the final menstrual period, after which prevalence declined slowly [43]. The median duration for vasomotor symptoms is 7.4 years, based on longitudinal data from SWAN [44], although there was wide individual variability in the timing of symptom onset, persistence, and daily frequency [45,46]. A survey of 40–65 years old individuals in Australia found that 6.5% of postmenopausal individuals aged 60 to 65 years continued to report vasomotor symptoms, showing that symptoms can persist over time in some individuals [47].

Hot flashes negatively influence daytime functioning, work productivity, mood, and sleep. A US population-based study of 2,703 postmenopausal individuals, aged 40–65 years old, found that 65% reported vasomotor symptoms (hot flashes/night sweats) in the past 4 weeks, with 7% having severe and frequent symptoms (seven or more symptoms in a typical day). Based on the menopause-specific quality of life questionnaire, vasomotor symptoms were associated with poorer quality of life across domains, in those with severe as well as mild/moderate vasomotor symptoms. Specifically, the presence of vasomotor symptoms had a moderate/extreme effect on work (46.0%), social activities (44.4%), leisure activities (47.6%), sleep (82%), mood (68.6%), concentration (69.0%), sexual activity (40.9%), total energy level (63.3%), and overall quality of life (69.3%), after adjusting for several sociodemographic covariates [48]. The group with severe vasomotor symptoms was more than three times more likely to report a negative impact on overall quality of life than was the group with mild/moderate symptoms (odds ratio 3.58; 95% confidence interval [2.23, 5.76]). Kingsberg and colleagues (2024) showed the relevance of considering concomitant vasomotor, mood, and sleep symptoms: in those with the triad of symptoms, 21.4% and 27.9% reported a substantial impact of vasomotor symptoms on work/study and overall quality of life, respectively, which was higher than the effect of vasomotor symptoms alone [49]. The effect of menopausal symptoms, including hot flashes, on occupation-related health constructs has received increasing attention, with studies showing that menopausal symptoms are strongly associated with poorer work performance, absenteeism, lower capacity to work [50], less work engagement and more emotional exhaustion, especially in those with more severe symptoms [3]. In the US, an annual loss of $1.8 billion has accrued based on workdays missed as a result of those symptoms [51]. Moderate and severe hot flashes are also linked to lower scores for health status [52], greater use of healthcare resources, and an increased risk for

cardiovascular disease in later life [53]. The presence and severity of hot flashes have been associated with higher blood pressure, poorer endothelial function and flow-mediated dilation, more aortic calcification, and a thicker carotid intima media [2].

As described below, hot flashes reflect an interaction between the female reproductive and thermoregulatory systems in the context of menopause. However, hot flashes can occur in some individuals in the reproductive stage, especially in those with premenstrual symptoms, during the late luteal phase when the levels of sex steroids begins to decline [54]. Indeed, it is not the levels of circulating estrogen but rather the rate of estrogen withdrawal that seems to determine the onset of hot flashes in natural menopause [36,55]. Abrupt oophorectomy (surgical menopause) results in severe and frequent hot flashes [56].

Endocrinology of the female reproductive system

In human females, the reproductive stage starts with the onset of the first menstrual cycle, called menarche, at around 12 years old [57] and ends with menopause, at around 45–55 years old [10]. The endocrinological changes that occur across the menopause transition are briefly presented here and are explained in more detail elsewhere [5,13,58]. Menopause is naturally embedded in the aging of the ovulatory system. Indeed, at around five months of gestational age, the ovaries produce a pool of several million follicles, and no further production occurs for the rest of life [58].

As described in detail by Reed and Carr (2000), the menstrual cycle is precisely coordinated through the actions of the hypothalamic-pituitary-ovarian axis [59]. During the follicular phase of each menstrual cycle, when sex steroid levels are low, gonadotropin releasing hormone (GnRH) is released into the hypothalamic-hypophyseal portal system, a system of blood vessels that connects the hypothalamus to the anterior pituitary. The release of GnRH is not continuous, but pulsatile in response to waves of depolarization in the GnRH neurons, which activate GnRH receptors in the anterior pituitary [60,61]. GnRH triggers the synthesis and release of the pituitary gonadotropins, FSH and luteinizing hormone (LH) [62]. In turn, FSH rises and induces the recruitment of a cohort of follicles in the ovaries (cycle days 1–4). The granulosa cells within the ovarian follicles produce AMH when stimulated by FSH, and AMH plays a role in the number of follicles in the recruited cohort. A competition starts between these follicles, resulting in the selection of typically one follicle (at around cycle day 5 to 7). The selected follicle becomes dominant, grows, and inhibits the growth of other follicles, which degenerate (from cycle day 8 onward). With the growth of the dominant follicle, granulosa cells produce increasing amounts of estradiol. The estradiol then enters the circulation and the GnRH pulse generator is generally inhibited by negative feedback from those ovarian sex steroids. Thus, the activity of the GnRH pulse generator decreases as estradiol levels increase. At mid-cycle, however, its feedback switches from negative to positive causing a spike in LH secretion from the pituitary and a surge in estradiol [63,64].

The LH surge enables the rupture of the mature follicle and release of the egg into the fallopian tube, a phenomenon called ovulation, typically occurring around the middle of the menstrual cycle (around cycle day 14). The luteal phase then starts, with the ruptured follicle degenerating into the corpus luteum. This structure continues to produce sex steroids, including progesterone, which in turn stimulates the vascularization and thickening of the endometrium for a potential pregnancy. The corpus luteum also produces inhibin B, which, together with progesterone, provides negative feedback on FSH and LH and inhibits the development of new follicles and their ovulation during the luteal phase. In the absence of pregnancy, the corpus luteum degrades, resulting in a drop in progesterone and inhibin B. Consequently, the endometrial lining sheds in a process called menstruation, marking the onset of a new menstrual cycle. In parallel, the drop in inhibin B also releases the inhibition on FSH, allowing the recruitment of a new cohort of follicles (cycle days 1–4) [59].

The ovulation process involves the recruitment and degradation of a number of follicles, which increases with age, from a finite reserve. By the time an individual reaches about 30 years of age, the number of follicles has diminished to approximately 12% of the initial pool [14], however, the hypothalamus, pituitary, and ovary display compensatory changes that

maintain follicle development, estrogen cycles, and overall, the reproductive capacity [58]. For example, with the decrease in ovarian secretions, including inhibin and AMH, the GnRH pulses become more powerful, with increased frequency, quantities produced, and pituitary sensitivity to GnRH. Also, the reduction in estradiol levels from the ovaries leads to a prolonged half-life of both FSH and LH. As a result, LH and FSH levels display a tenfold and fifteenfold increase, respectively (Figure 1) [13]. By about 40 years of age, the pool has decreased to around 3% of the original reserve [14]. Progressively, those compensatory mechanisms become insufficient to compensate for the sustained follicle loss, and cycles become irregular. At about 50 years of age, the reserve is nearly exhausted, falling below 1,500 follicles. With this progressive depletion of the ovarian reserve, as well as the decrease in oocyte quality, menstrual cycles are more and more disrupted until they cease permanently, marking menopause [13,58].

Control of the reproductive system and the role of KNDy neurons

While the negative feedback that is supplied by gonadal steroids is an important determinant of the activity of GnRH neurons in the hypothalamus, that feedback is finely tuned by other signals. Various signals, such as kisspeptin, norepinephrine, and neuropeptide Y, cause stimulatory modulation of the activity of GnRH neurons in several species including humans [65,66]. Others, such as the endogenous opioid peptide dynorphin (DYN) and interleukin-I [67], seem to provide inhibitory modulation of the activity of GnRH neurons.

The general operation of the reproductive cycle has long been known, but only relatively recently has the mechanism of steroid feedback been clarified. There was always a gap in descriptions of the system, because GnRH neurons in the hypothalamus do not express the estrogen receptor α (ERα) to which estradiol binds [19,68]. While Rance and Young (1991) showed in the early 1990's that neurons containing ERα and neurokinin B (NKB) in the human infundibular (arcuate) nucleus (abbreviated here as the ARC) were involved in estrogen negative feedback, a mechanism for the feedback of sex steroids on GnRH neurons was revealed only with the discovery of the importance of the neuropeptide kisspeptin and one of its receptors (G-coupled protein receptor; GPR54) in humans and mice [19,66,69,70]. Recent literature commonly refers to kisspeptin receptors as Kiss1R.

Kisspeptin neurons that also express NKB, glutamate, and DYN, the so-called KNDy neurons in the ARC of several species, including humans, express ERα [71,72] and are glutamatergic [73]. The activity of those KNDy neurons in the ARC is modulated negatively by circulating estradiol that binds to ERα, such that the activity of those KNDy neurons is relatively low with exposure to estradiol, but relatively high when estradiol is absent, such as after ovariectomy. In human females, as well as in rodents, goats, and sheep, when estradiol levels are low, the KNDy neurons release kisspeptin that then binds to nearby kisspeptin receptors (GPR54 [66]) on GnRH neurons and depolarizes them [71,72,74–82]. But when estradiol levels are high, the KNDy neurons are inhibited and the GnRH neurons are not activated, thus closing the negative feedback loop between the brain and the gonads [83–85].

As such, the KNDy neurons are intermediary neurons that provide the feedback link between sex-steroids and the GnRH neurons, without the steroids interacting directly with those GnRH neurons. The KNDy neurons are now recognized as central modulators of GnRH activity and subsequent GnRH secretion [66,69,80,81,86]. Normal ovarian function is determined by the pattern of LH pulses from the pituitary, which in turn depends on the pattern of GnRH pulses from the hypothalamus. Wilson and coworkers (1984) detected pulses of synchronized electrical activity in the ARC of the rhesus monkey that timed with LH pulses and proposed the idea of the "GnRH pulse generator" [70,87]. Since then, further compelling evidence has emerged that the source of the electrical activity that generates these GnRH pulses is the network of KNDy neurons [69,71,72,78–82,85,86].

The connection between GnRH neurons in the preoptic area and KNDy neurons

With menopause in women, there is about a 50% increase in the expression of the GnRH gene in the medial basal hypothalamus (MBH) [88]. The

increase in GnRH expression during menopause does not occur in all neurons that express and release GnRH and is region specific in women [88], as it is in ovariectomized rats [89]. Using immunohistochemical techniques, Borsay and coworkers (2014) found that GnRH neurons in the MBH of the postmenopausal human female are situated close to KNDy neurons, and the axons of those GnRH neurons project along the infundibular stalk to the posterior pituitary gland [90]. The KNDy neurons do not form synaptic or dendritic connections with the GnRH neurons but remain in close apposition with those neurons. In rodents, a majority of the cell bodies of GnRH neurons are located in the preoptic area (POA) of the brain, with their nerve terminals located in the median eminence [91]. Although dendro-dendritic interaction is frequent between GnRH neurons, the activity of GnRH neurons is influenced by neighboring non-GnRH neurons [90,92], including the KNDy neurons mentioned above (Figure 2).

In humans, as well as projecting to GnRH neurons in the MBH, KNDy neurons project to the soma of GnRH neurons in the POA (See Figure 2) [100,101]. The KNDy neurons that are located in the ARC co-release kisspeptin, NKB, glutamate, and DYN in several species, including humans [73,91,102–107]. The KNDy neurons in the ARC project extensively within the ARC to other KNDy neurons and to the contralateral ARC, where they create an interconnected complex via the expression of the receptor for NKB (neurokinin-3 receptor; NK_3R), in several species including humans [90,91,108–110] and via the expression of the glutamatergic receptor AMPA [73,102,106,107,111–114] (Figure 2).

The KNDy neurons do not express receptors for kisspeptin [66], however, the stimulatory NKB and the inhibitory DYN act on NK_3R and on the κ-opioid receptor (KOR), respectively, which are expressed on the KNDy neurons themselves [105]. As such, the KNDy neurons synapse to one another [114,115] in an inter-connected network that is capable of producing synchronized episodic firing activity [73,103,111,116]. Furthermore, as mentioned above, KNDy neurons make abundant close, but non-synaptic, appositions with the GnRH somata in humans [90,100,101] and with the GnRH dendrons in rodents [91]. Dendrons are long dendrites that receive synaptic input but that also propagate action potentials, just like axons [117].

The synchronized episodic activity of KNDy neurons is thought to be controlled by recurrent glutamate, NKB, and DYN expression, and the release of kisspeptin from the KNDy neurons onto the GnRH somata or dendrons which consequently results in the release of GnRH [66] in several species including ruminants, humans and rodents [71,82,95,111,118,119]. The episodic release of GnRH from the GnRH neuron and the recurrent release of neuropeptides at the cluster of KNDy neurons are driven through differential post-synaptic receptor expression at the GnRH neuron somata and/or the GnRH dendron (GPR54 for kisspeptin) depending on species, and at the KNDy neuron somata (AMPA for glutamate, NK_3R for NKB, and KOR for DYN) [80,82,111].

According to the "Dale principle" the same set of neuropeptides will be released by all axons of an individual neuron [120]. This principle was proved wrong for small molecule co-expression by Tritsch and coworkers (2016), while Voliotis and coworkers (2021) proved it wrong for, at least part of, the KNDy neuron [73,121]. The neuropeptides that are expressed by the KNDy neuron are packaged individually and separately in synaptic vesicles and are differentially released [82,121,122]. All of the neuropeptides that are released from the KNDy neuron, except kisspeptin, are active post-synaptically at the somata of the same KNDy neuron and of other KNDy neurons in that KNDy network, whereas the only neuropeptide that is active post-synaptically at the GnRH dendron is kisspeptin [82,105,106,123,124]. As such, the uniform transmission of kisspeptin to its primary efferent target, the GPR54 receptor on the GnRH dendron, still conforms to the theory behind Dale's principle, whereas the release of glutamate, NKB, and DYN does not. When kisspeptin was selectively deleted from KNDy neurons in mice, the pulsatile secretion of GnRH from the GnRH neuron failed, however, the episodic activity of the glutamatergic KNDy neurons that is driven by the recurrent release of glutamate, NKB, and DYN, was maintained [82]. This finding led the authors

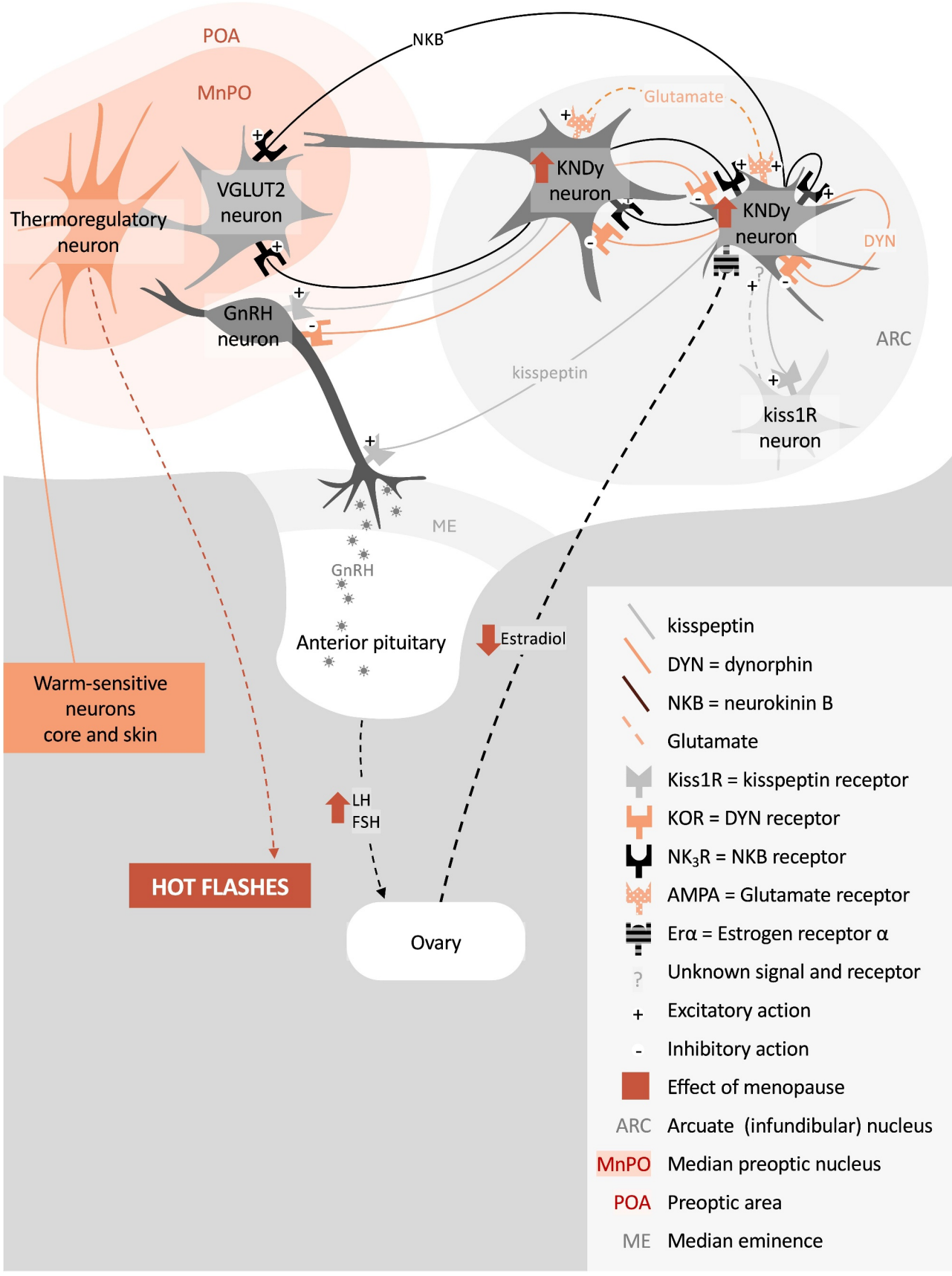

Figure 2. Schematic of the relationship between KNDy neurons in the ARC and glutamatergic neurons (VGLUT2 neurons; vesicular glutamate transporter 2) in the MnPO in the central heat defense pathway, and GnRH neurons of the POA in the central reproductive

to conclude that the differential expression of receptors for those neuropeptides post-synaptically at the KNDy neuron and the GnRH dendron drives pulsatile hormone secretion via the co-transmission of neuropeptides from the KNDy neurons. As such, different patterns of post-synaptic receptor expression at the targets of the KNDy neuron, the KNDy somata, and the dendrons of GnRH neurons, is required for the synchronized episodic release of GnRH [82].

It was discovered recently that glutamate-AMPA signaling contributes to the synchronized activity of the KNDy network [73,111]. The blockade of glutamatergic AMPA receptors on KNDy neurons *in vivo* in mice resulted in a decrease in GnRH, and therefore LH, pulse frequency [73]. The inhibition of the GnRH pulse frequency was resolved by optic stimulation of that KNDy population, indicating that the pulse generation activity of the KNDy network depends on the activity of glutamate-AMPA signaling and the level of network excitability [73]. The work of Voliotis et al. (2021) further indicated that pulse generation in the KNDy neuron network in the ARC depends not only on the basal and exogenous activity of the individual neurons in the network, but also on the ability of those KNDy neurons to signal and communicate with each other. In vitro studies using calcium imaging have suggested that glutamate driven synchronization in the KNDy neuron network is potentiated by NKB, while DYN may have a modulatory gating role, at least in mice, in that initiation of glutamate-driven synchronization is blocked by DYN [111]. Thus, the co-release of DYN acts as a modulator of the kisspeptin-mediated release of GnRH in mice [72].

These findings led Moore and coworkers (2024) to suggest that the role of NKB in pulse generation depends on the excitability of the KNDy neuron network that is mediated by glutamate-AMPA signaling and the steroidal tone of that network [80]. The level of excitability of the KNDy neurons is key to signal and to activate each neuron in the KNDy neuron cluster [111]. NKB and glutamate seem to act in an auto synaptic fashion via projections between KNDy neurons that synchronize the activity of the entire KNDy neuron network [80]. Thus, glutamate, NKB, and DYN signaling within the KNDy neuron network in the ARC generate episodes of synchronized KNDy neuron activity that is relayed to the GnRH neuron through kisspeptin [80].

Within the KNDy neuron network, recent novel evidence points toward a role for non-KNDy neurons in the ARC that express another kisspeptin receptor, Kiss1R [94]. In sheep, when neurons in the ARC that express Kiss1R were ablated, the variability of LH pulses was increased, while the amplitude of the pulses was decreased [94]. Importantly, the pulses were not eliminated. In contrast, when KNDy neurons were ablated in the ARC, LH pulses were almost completely eliminated [94]. These findings suggest that, at least in sheep, a positive feedback loop exists between ARC Kiss1R neurons and the KNDy neuron network that drives the episodic activity of the GnRH

pathway. During menopause, declining levels of estradiol cause hypertrophy of KNDy neurons, which become hyperactive [71,93]. Depolarization of KNDy neurons leads to the release of kisspeptin, which activates the non-KNDy Kiss1R expressing neurons in the ARC, at least in sheep [94]. These neurons release a stimulatory signal back to an, as of yet, unknown receptor on the KNDy neurons, which further stimulates the release of neuropeptides in a positive feedback circuit [80]. The release of NKB and glutamate activates the KNDy neuron network and elicits a synchronized episodic release of kisspeptin, which targets kisspeptin receptors on the soma of GnRH neurons in the MBH in humans and sheep, and the GnRH dendrons in the median eminence in rodents, initiating the pulsatile release of GnRH, with downstream release of LH and FSH, resulting in estradiol production in the ovaries in several species, including humans [66,69,71–73,78,80]. Depending on species, with a brief time lag, the cycle of events that leads to the release of GnRH is terminated by the release of DYN exerting an inhibitory action via KOR on the synchronized activity of KNDy neurons, that terminates the release of glutamate, NKB, and kisspeptin and hence ends the GnRH pulse [80,95,96]. DYN may also act directly on the GnRH soma via KOR, terminating the GnRH pulse in ruminants and rats [97]. When NKB is released in rodents, it also targets VGLUT2 neurons in the MnPO that express NK_3R. Depolarization of those VGLUT2 neurons triggers the release of glutamate, which slightly depolarizes adjacent thermoregulatory neurons, thus sensitizing those neurons by bringing them closer to the threshold for an action potential [98,99]. We hypothesize that similar occurs in humans, and that those thermoregulatory neurons thus become more sensitive to afferent input from warm-sensitive neurons in the periphery and core. Triggering of the thermoregulatory neurons activates the heat defense pathway, resulting in cutaneous vasodilation and heat dissipation, i.e. The hot flash.

pulse generator. It is unknown whether Kiss1R neurons play a similar role in the ARC of humans.

When the signaling provided by NKB and glutamate drive the membrane potential of the projections from those same KNDy neurons that contain vesicles of kisspeptin to their threshold, there is a synchronized episodic release of kisspeptin from those KNDy projections onto the apposing GnRH neurons [82,106,111]. The stimulatory kisspeptin acts on the kisspeptin receptor GPR54 in proximity to the secretory zone of the GnRH neuron in the ME/MBH in several species, including humans [69,81,82]. The cell bodies of GnRH neurons are found throughout the POA and the hypothalamus, and the convergence of GnRH dendrons in close apposition with KNDy neurons constitutes a setting in which the pulsatile release of kisspeptin from KNDy neurons leads to the pulsatile release of GnRH [82,125]. As such, the depolarization of KNDy neurons leads to the secretion of glutamate and NKB that stimulates and synchronizes KNDy neuron activity via AMPA and NK_3R that ultimately stimulates the synchronized, episodic, release of kisspeptin from the KNDy neuron network. The pulsatile depolarization of the GnRH neuron via kisspeptin stimulates the pulsatile release of GnRH [105,126] and consequently, the downstream release of LH (Figure 2) [119]. Moore and coworkers (2022) found that pulses in the KNDy neuron network always preceded the LH pulse in a series of *in vivo* single cell experiments in mice [119]. It seems plausible that the synchronized episodic activity of the KNDy neuron network, facilitated by the oscillating slow positive (glutamate and NKB driven) and negative (DYN/?) feedback that drives the episodic release of kisspeptin and consequently the downstream pulsatile release of GnRH (and then LH), is the source of the "GnRH pulse generator" [85,111,119].

The question of how the synchronized activity of the KNDy neuron network, and subsequent kisspeptin release, is terminated remains largely unresolved. In ruminants, the GnRH pulse is ended by the release of the inhibitory DYN that acts on KOR receptors on the KNDy neurons [95,96,118]. DYN may also act directly on the GnRH soma via KOR to terminate the GnRH pulse in ruminants and rats [97]. While DYN has a clear inhibitory role in pulse generation in ruminants, its role varies greatly between species, and is unclear in rodents [80,111] and primates, including humans [80,127]. Only a small percentage of KNDy neurons express DYN in the ARC in female rhesus macaques [128] and in postmenopausal women [129]. Recent work in mice by Han and colleagues (2023) points toward a role for calcium-activated potassium channels within the KNDy neurons [111]. The opening of these potassium channels hyperpolarizes the KNDy neuron at times of recurrent activation. This limitation of sustained KNDy neuron firing would be accompanied by reduced glutamate and NKB release, possibly bringing an end to the pulsatile action, at least in mice [111]. Similarly, the physiological role of glutamate and its receptor AMPA in pulse generation in primates, including humans, remains to be explored.

The importance of the KNDy neurons for human reproduction is highlighted by the findings that mutations of NKB, NK_3R, or kisspeptin-derived peptide receptor, are associated with hypogonadotropic hypogonadism [130–132].

Hypothalamic changes with menopause

Several changes to the structure and function of the human hypothalamus have been measured after menopause. Postmortem analysis of the hypothalamus from before to after menopause has revealed changes in humans that mirror the changes that are observed in ovariectomized animals [20]. The major change is hypertrophy of KNDy neurons in the ARC [19,20,93,133] An early study identified that neurons in the ARC that express the estrogen ERα were hypertrophied in post-menopausal women [71]. Later studies showed that those same hypertrophied neurons express NKB and kisspeptin, and that there was higher expression of the genes for NKB and kisspeptin in those hypertrophied neurons in postmenopausal women and ovariectomized monkeys [19,134], and that replacement of estrogen reversed those changes [134–136]. Together the findings indicate that the neuronal hypertrophy and increased gene expression of NKB and kisspeptin are secondary to the decrease in estrogen levels that accompany menopause [134–137]. Rometo and coworkers (2008) also reported

hypertrophy of DYN expressing neurons in the ARC in postmenopausal women, but there were fewer neurons expressing DYN mRNA in the ARC of those women compared to pre-menopausal women [138].

An immunohistochemistry study showed that in postmenopausal women a high quantity of kisspeptin and NKB fibers innervate the projections of hypophysiotropic GnRH neurons [90]. While there was no difference between pre- and postmenopausal women in the expression of the GnRH gene in the dorsal preoptic-septal region, expression of the GnRH gene was 50% higher in the MBH in menopause [88]. These changes all occurred with no change in the estrogen negative feedback mechanism from pre- to post-menopause [139–141].

The thermoregulatory system

The thermoregulatory network consists of a central integrative circuit located mainly in the POA of the hypothalamus, which orchestrates the activation of thermoeffector mechanisms in response to input from central and peripheral thermoreceptors [142]. That system maintains core temperature (T_{core}) at a median of about 36.7°C, with a range of ±0.5°C, and with a circadian period of just over 24 h [143]. Core temperature refers to the temperature of deep-body tissues; sites for T_{core} measurements include the esophagus, rectum, and abdomen (via telemetric pills passing through the digestive tract) [143]. Thermoregulatory responses to heat are stimulated by input from warm-sensitive neurons in the periphery (especially the skin, but also the spinal cord, muscles, and abdominal area) to the hypothalamus, or by input from warm-sensitive neurons in the hypothalamus itself [144]. The warm-sensitive name derives from the fact that the firing rate of these neurons increases with warming. Changes in T_{core} strongly activate thermoeffectors through negative feedback, while the surface temperature, mainly from the non-glabrous (hairy) skin, constitutes an auxiliary signal [145–147]. The glabrous (non-hairy) skin such as the palms is specialized in sensing the temperature of local objects and informing subsequent behaviors [146]. However, it contributes only marginally to the feedback to the thermoregulation process described below [146].

Another class of afferent neurons, the so-called cold-sensitive neurons, that increase firing rate with cooling, activate responses to cold exposure. When the input from cold-sensitive neurons reaches a threshold, either shivering or non-shivering thermogenesis is activated and the production of metabolic heat increases. The ambient temperature (T_a) at which that activation occurs is called the lower critical temperature, and it defines the lower margin of the thermoneutral zone (TNZ) [148]. The upper margin of the thermoneutral zone is called the upper critical temperature and it is defined as the T_a above which active evaporative heat loss (sweating in humans) is activated [149]. Within the TNZ, thermoregulation is achieved by the control of blood flow to the skin, mediated by the release of norepinephrine onto arterioles in the peripheral vascular system that causes vasoconstriction, i.e. within the TNZ temperature regulation depends only on the control of sensible (dry) heat loss. In normal circumstances, that sympathetic vasoconstrictor system is fully activated at the lower critical temperature, and silent at the upper critical temperature, with a grade of activation in between.

In several studies that have investigated hot flashes, instead of measuring the *ambient* temperature thresholds, the *core* temperature thresholds at which shivering and sweating were triggered have been measured [18,21–25]. That zone is often referred to as the inter-threshold zone, but in some papers, it was called the TNZ. For clarity, here we refer to the zone between *ambient* temperature thresholds as the TNZ, and the zone between *core* temperature thresholds as the inter-threshold zone.

At the upper critical temperature, or when the input to the regulatory system from warm-sensitive neurons reaches the upper limit of the inter-threshold zone, heat defense mechanisms, including active vasodilation and sweating, are activated. Active vasodilation of blood vessels in the skin leads to an increase in skin blood flow beyond that achieved by the silencing of active vasoconstriction. Active vasodilation is mediated by sympathetic cholinergic neurons that also release other vasodilator co-transmitters, including

nitric oxide [150]. The vasodilation response increases the delivery of warm arterial blood to the skin, where heat is lost to the environment whenever T_a is lower than skin temperature (T_{skin}). The activation of sweating is also mediated by sympathetic cholinergic neurons, and acetylcholine is the active neurotransmitter for the response [150]. The human sweating response leads to the removal of large quantities of heat (~73 kJ·min^{-1}) from the skin when the sweat evaporates [151]. Whether there is one set of cholinergic neurons that activates both sweating and active vasodilation, or separate systems of cholinergic neurons that drive the two responses, remains equivocal [150]. In combination, those responses "close the loop" in the negative feedback control of T_{core}, because by increasing the removal of heat from the body and decreasing the body heat content, T_{core} is lowered and the input from the warm-sensitive neurons that initially activated the response will decrease.

In the traditional view of behavioral thermoregulation the input signals from thermosensors that motivated thermal behavior were thought to project to the somatosensory cortex, where a conscious perception of thermal status was formed and changes in behavior were motivated. Evidence in support of that scenario was that, while lesions to the pre-optic anterior hypothalamus prevented the stimulation of autonomic thermoregulatory responses in mammals, those lesions did not disrupt behavioral responses to cold [152]. In that traditional view, inputs from peripheral thermosensors were thought to project, via second-order sensory neurons of the ascending spinothalamic tract, to the thalamus and further relayed to the somatosensory cortex where the perception of temperature is formed, and presumably behavioral responses are initiated. Those same second-order sensory neurons also project via the lateral parabrachial (LPB) nucleus to the POA of the hypothalamus, where autonomic responses are initiated [153]. But in 2016, Tan identified a subset of neurons in the hypothalamus (specifically in the anterior ventromedial preoptic area) of mice that respond to warming of the periphery [154]. As was expected, optogenetic depolarization of those neurons inhibited the activation of brown adipose tissue and resulted in tail vasodilation, both of which are normal autonomic responses to increasing T_a. But the activation of those anterior ventromedial preoptic area neurons also resulted in the mice selecting lower environmental temperatures and inhibited the nest-building behavior that is normally characteristic of mice exposed to cold. Hence, behavioral responses to heat were generated by neurons in the hypothalamus, with no apparent involvement of the thalamus, or cortical areas that are usually associated with the behavioral response. Later, Yahiro and coworkers (2017) showed that rats with ablation of the spinothalamocortical pathway exhibited normal cold- and heat-avoidance behavior, indicating that behavioral thermoregulation could occur in the absence of the cortical perception of T_{skin} [155]. But when the lateral parabrachial nucleus was ablated, the rats no longer exhibited cold- or heat-avoidance behavior. Yahiro et al. concluded that the lateral parabrachial nucleus, and not the thalamus, mediates the signaling from cutaneous thermosensory neurons that is required for behavioral thermoregulation [155]. Similarly, Almeida and coworkers (2006) showed that neuronal bodies in the dorsomedial hypothalamus, and axons passing through the paraventricular nucleus of the hypothalamus, were required for rats to exhibit the cold-seeking behavior that is characteristic of the response to a large dose of bacterial LPS, and subsequent endotoxic shock [156]. In a recent review, Morrison and Nakamura (2019) concluded that "How the thermosensory signals conveyed to the POA contribute to the generation of thermal comfort and discomfort that motivate behavioral thermoregulation remains to be understood" [157].

Integration between the thermoregulatory and reproductive systems: How hot flashes are triggered

The POA of the hypothalamus contains a population of neurons that receive afferent temperature signals from the periphery and viscera. Those neurons trigger a series of autonomic and behavioral thermoregulatory responses to changes in the afferent thermal input (Figure 2) [154–160]. For example, an increase in thermosensory information from warm-sensitive neurons activates

heat defense mechanisms including cutaneous vasodilation, sweating, and cold-seeking behavior [137]. KNDy neurons project from the ARC to key thermoregulatory areas within the POA, the median preoptic nucleus (MnPO) and the medial preoptic area, and those KNDy neurons co-express NKB [104,105,108,110,118]. The NKB signaling pathway in the MnPO plays a key role in menopausal hot flashes [109,137].

As described above, the activity of KNDy neurons is inhibited by circulating estradiol [161]. With menopause, estrogen levels decrease and the KNDy neurons in the ARC begin to hypertrophy along with, in humans at least, an increase in the expression of kisspeptin and NKB [19,20,26]. Similar changes occur following ovariectomy in primates [20,162], rats [83], sheep [104], and mice [75]. In a landmark study, Jayasena and coworkers (2015) infused pre-menopausal women with NKB [163]. The women reported the sensation of hot flashes that were accompanied by an increase in T_{skin} along with elevated heart rate, similar to the changes observed during a menopausal hot flash [163]. In support of an important role for NKB, antagonism of NK_3R in post-menopausal women reduced the frequency of hot flashes [164]. Combined with the results of the genome-wide association studies mentioned above by Crandall and coworkers (2017), that variation in the gene for TACR3 (which codes for NK_3R) is associated with the occurrence or not of hot flashes [42], evidence is growing for an important role for NKB in hot flashes and that there is a genetic component to the probability of developing hot flashes with menopause.

The KNDy neurons in the human ARC co-express ERα and NKB [71]. Borsay and coworkers (2014) showed that when the GnRH tract descends through the infundibular stalk to the posterior pituitary gland in women, it is exposed to dense plexuses of NKB fibers [90]. Expression of the NKB gene increases with menopause and/or oophorectomy in humans and is associated with hypertrophy of those neurons that express NKB [20,71]. In monkeys and rats, ovariectomy leads to an increase in expression of the NKB gene, and that increase is reversible with estradiol treatment [20,165]. Rance and coworkers proposed that an increase in the activity of KNDy neurons when circulating estrogen decreases after menopause could be a mechanism for the generation of hot flashes [137]. That hypothesis found support when Padilla and coworkers (2018) showed that artificial activation of KNDy neurons in the ARC in mice caused an increase in skin temperature on the tail ($T_{skin,tail}$), followed by a transient decrease in T_{core}, providing evidence of a heat dissipation response [109]. The activation of KNDy neurons in mice led to an increase in neuronal activity in the temperature effector region of the POA, as evidenced by elevated c-fos expression (which is a transsynaptic marker of increased neuronal activity [166]) in the POA when the KNDy neurons were stimulated [109]. Even a brief activation of the circuit of KNDy neurons elicited a prolonged heat loss response. Thus, KNDy neurons appear to relay information to the warm-sensitive pathway in the POA, and activation of those KNDy neurons can result in symptoms similar to those seen with hot flashes. KNDy neurons become more active after the acute withdrawal of sex hormones in mice by gonadectomy, and those changes seem to mirror the changes that occur with menopause [167]. The findings of Padilla and coworkers suggest that the altered properties of hypertrophied KNDy neurons in the ARC in menopausal individuals results in a sensitized vasomotor response to the stimulation of KNDy neurons [109], thus contributing to a susceptibility to hot flash.

KNDy neurons that express NK_3R are present in the ARC and the MnPO in rodents [168]. It is now generally accepted that the release of NKB from those KNDy neurons provides a mechanism that links the endocrine changes that occur with menopause to the vasomotor symptoms of hot flashes [42,164,169]. In mice, the infusion of a NKB antagonist into the POA, prior to activation of KNDy neurons in the ARC, prevented the increase in $T_{skin,tail}$ that normally occurred after the activation of KNDy neurons in the ARC [109]. The generation of increases in $T_{skin,tail}$ in mice was also completely abolished by the infusion of an NKB antagonist into the MnPO, which suggests that NKB release from the KNDy neurons in the ARC that project to the MnPO is the central pathway for the generation of hot flashes (Figure 2) [110].

Thus, it is hypothesized that the activity of estrogen-sensitive KNDy neurons in the ARC

contributes to the generation of hot flashes in menopausal individuals via axonal projections to NK_3R expressing neurons in the MnPO [98,109,137]. In female mice, the ablation of NK_3R neurons in the MnPO resulted in an increase in T_{core} that persisted despite changes in T_a and irrespective of estrogen status, suggesting that the NK_3R system is important in heat defense generally, at least in mice, not just in hot flashes in menopausal women [98]. The general system seems to be similar in rats, because the infusion of senktide, an NK_3R agonist, into the MnPO caused neurons in the MnPO to become active, as measured by the c-fos method, and resulted in a decrease in T_{core} [170]. Krajewski-Hall and coworkers (2019) found that in mice 94% of the neurons that express NK_3R in the MnPO were glutamatergic [98]. Ablation of the neurons that express NK_3R in the MnPO abolished the effect of senktide on T_{core} [99], indicating a role for glutamatergic neurons in the MnPO in mechanisms of heat dissipation [171].

When mice and rats are exposed to an increase in T_a or in T_{core}, there is an increase in fos activity in the MnPO [109,170]. But when fos activity was measured specifically in glutamatergic neurons that express NK_3R in the MnPO, there was no change [98]. Those neurons that express NK_3R in the MnPO are therefore not warm-sensitive neurons and nor are they activated by input from warm-sensitive neurons in the periphery or the viscera. Krajewski-Hall and coworkers (2019) concluded that, at least in rodents, KNDy neurons must activate heat dissipation effectors indirectly of warm-sensitive neurons via a population of glutamatergic NK_3R neurons (vesicular glutamate transporter 2 neurons; VGLUT2) in the MnPO that excite other neurons that are part of the central heat defense pathway (Figure 2) [98].

For a long time it was thought that the close temporal relationship between an LH surge and a hot flash was causal. But with the discovery of the KNDy mechanism, that association has been shown to be just that, an association. With the menopause-related decrease in circulating estradiol, there is an increase in the expression of kisspeptin and NKB in KNDy neurons in the ARC. In turn, that priming of the KNDy neurons then elicits GnRH release via kisspeptin signaling, and thus the release of LH, as well as hot flashes via NKB signaling to glutamatergic NK_3R neurons that modulate the activity of heat-effector neurons in the MnPO [109,137,172]. That mechanism explains the close temporal relationship between an LH pulse and a hot flash. Further evidence that the role of LH is simply a temporal association is that while an increase in plasma LH is detected with most hot flashes in women, the increase in LH does not precede the flash [119,173–175], and hot flushes can still occur in women in whom LH pulses have been abolished by pituitary desensitization [176].

As well as input from warm-sensitive neurons, a hot flash can be triggered in symptomatic individuals by sensory and interoceptive cues, including anxiety, altitude, and other acute physiological stressors. Apart from the finding that the ablation of NK_3R neurons in the MnPO of female mice resulted in an increase in T_{core}, the functional relevance of KNDy innervation in the MnPO for normal thermoregulation has not, to our knowledge, been elucidated. Padilla and coworkers (2018) suggested that the hypertrophic state of KNDy neurons in the ARC during menopause may activate NK_3R in the MnPO without any functional significance under normal conditions [109].

Characteristics and physiology of hot flashes

A hot flash is a vasomotor symptom consisting of a heat dissipation response, typically lasting between one and five minutes, involving vasodilation and sweating [18,177]. Sweating occurs during 90% of perceived hot flashes [18] and there is approximately a twofold increase in sternal and forearm skin blood flow during a hot flash. In association with peripheral vasodilation, T_{skin} increases during a hot flash, and that increase is detectable in glabrous skin such as that of the fingers, toes, and forehead, and in non-glabrous skin such as that on the forearm and thigh [18]. A hot flash is accompanied by a 4-fold increase in skin sympathetic nerve activity, which returns to baseline after the hot flash [177]. When the release of neurotransmitters from sympathetic cholinergic nerves is blocked via the intradermal injection of botulinum toxin in the forearm and forehead, the

change in skin blood flow during a hot flash is attenuated [177]. These findings suggest that increased peripheral vasodilation during a hot flash is neurally mediated primarily via sympathetic cholinergic neurons that are responsible for cutaneous active vasodilation [177]. A hot flash is also accompanied by cardiovascular changes, including an increase in heart rate that is detectable before the onset of sweating, and a decrease in mean arterial pressure, at least in some individuals [177,178]. An increase in heart rate and decrease in blood pressure is also evident during hot flashes that occur in undisturbed sleep [179]. While there is no increase in T_{core} (measured as esophageal temperature) in the 2-min period before a hot flash, a clear decrease in T_{core} typically is evident following a hot flash, as sweating and cutaneous vasodilation dissipate heat [18,175]. Physiological changes that have been recorded around the onset of a hot flash are presented in Figure 3.

The inter-threshold zone and hot flashes

While the majority of individuals who transition to menopause experience hot flashes, some do not, and others have a very low frequency of hot flashes. That has led researchers to look for differences between symptomatic and asymptomatic individuals, to elucidate the mechanisms of a hot flash. In a series of studies, Freedman and colleagues employed peripheral warming, consisting of placing warming pads on the torso of participants to increase their body temperature, to provoke hot flashes. The technique proved successful in provoking hot flashes in 8 of 11 symptomatic individuals within 30 minutes of warming [22]. In response to the same stimulations, no hot flashes were measured in either premenopausal or asymptomatic post-menopausal participants [18,21,22]. With these experiments of body heating, Freedman investigated whether there is a difference in the threshold for sweating between symptomatic and asymptomatic individuals (reviewed in Freedman [18]). Sweating occurred at a lower T_{core}, as measured with an ingested telemetry pill, in symptomatic (37.2 ± 0.09°C, $n = 12$) than in asymptomatic (37.5 ± 0.14°C, $n = 8$) individuals [23]. There was no difference in the T_{core} at which shivering began when exposed to a cold environment in symptomatic (37.2 ± 0.15°C) and asymptomatic (37.1 ± 0.09°C) individuals [23]. These data revealed a narrower inter-threshold zone (0.0 ± 0.11°C) in symptomatic than in asymptomatic (0.4 ± 0.18°C) individuals [23], with the difference due mainly to a lowering of the threshold for heat loss. Freedman and Krell hypothesized that a slight elevation in T_{core} before a hot flash could be the trigger in symptomatic individuals, with these individuals having a lower threshold for the induction of heat dissipation [23]. Indeed, in support of this hypothesis, they demonstrated a small but significant increase in T_{core}, as measured with an ingested radiotelemetry pill, in the 30-minutes prior to a hot flash, in about two-thirds of the study participants (Figure 3) [24,182], although they acknowledged that an increase in T_{core} cannot be the sole trigger [182] since it was not detected in the remaining one third of hot flashes. Measures of rectal and esophageal temperature did not capture this increase prior to the hot flash [18], which the authors hypothesized was because temperatures at these sites varied more slowly than did gastrointestinal temperature. However, the hypothesis that an elevation in T_{core} in individuals with a low threshold triggers a hot flash has been challenged. A study by other investigators that used similar methodology including tracking of T_{core} with an ingested radiotelemetry pill in 34 postmenopausal individuals, found that only 51% of the hot flashes detected, based on a measure of sternal sweat rate, were preceded by any increase in gastrointestinal temperature, with the increase being, on average, 0.03°C. Additionally, when trying to provoke hot flashes by increasing T_{core} using mild heating, increases in gastrointestinal temperature of an average of 0.15 ± 0.17°C, which is substantially greater than 0.03°C, did not necessarily provoke a hot flash [180], suggesting that T_{core} does not consistently increase before every hot flash, and that an elevation in T_{core} of 0.03°C or more does not guarantee the occurrence of a hot flash. Further, this study observed similar temperature thresholds for the onset of sweating in response to whole body passive heating between symptomatic postmenopausal and young, premenopausal individuals [180], challenging the idea that thresholds for sweating are lower in individuals symptomatic for hot flashes. Alternative explanations for the trigger for a hot flash include that it could be non-thermoregulatory, such as involving the sympathetic nervous system, or that the trigger is thermoregulatory but involves instability in the system such that the threshold for sweating transiently changes and triggers

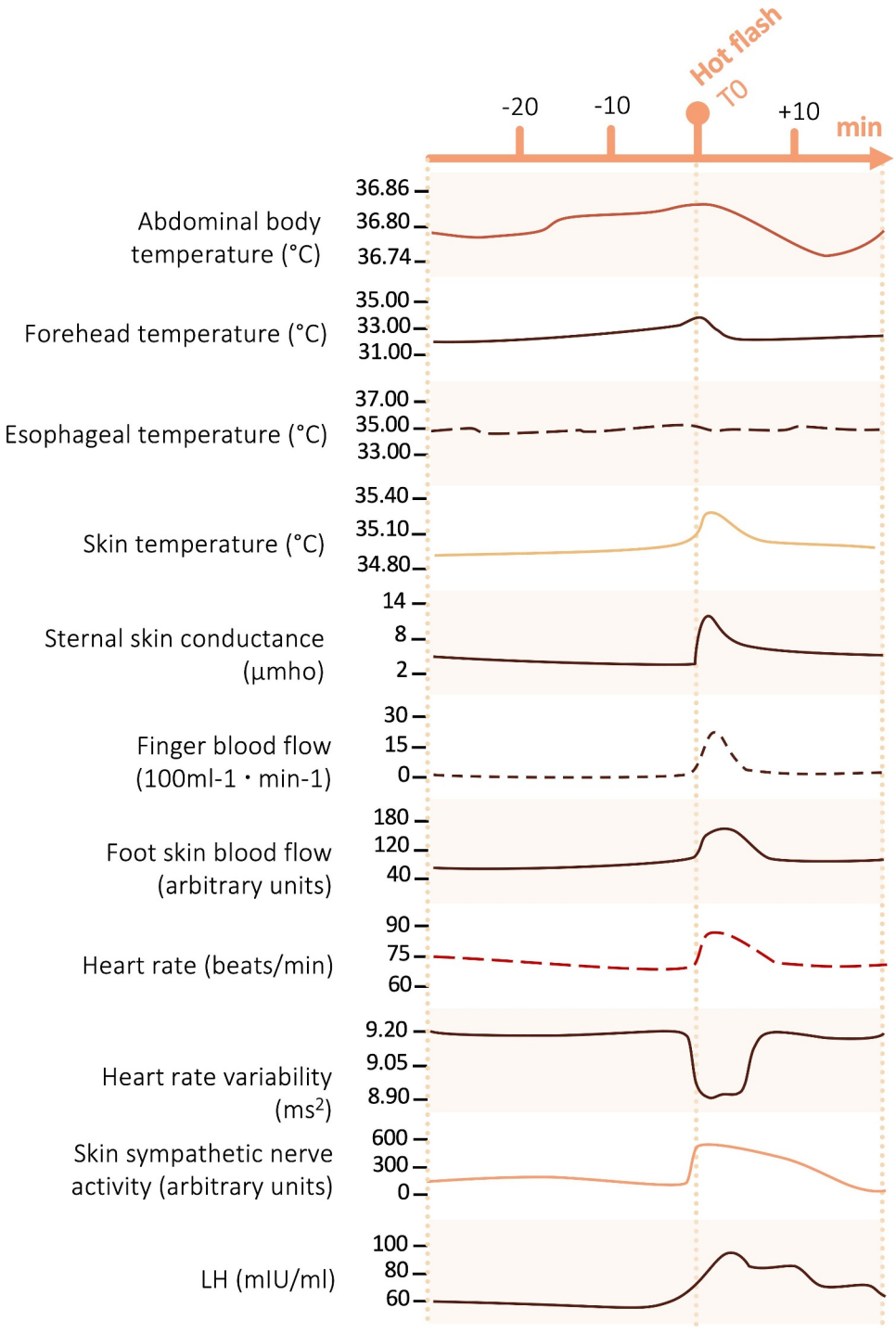

Figure 3. Schematic figure of the physiological changes that occur during a hot flash. Changes in variables are shown for 30 minutes leading up to, and 20 minutes after, a hot flush for abdominal body temperature [18] (although also see [180], which did not find this increase), forehead skin temperature [175], esophageal temperature [175], mean skin temperature calculated from thermistor probes on the chest, upper arm, thigh, and lower leg [18], sternal skin conductance [18], finger blood flow [175], foot skin blood flow [177], heart rate [175], heart rate variability [53], skin sympathetic nerve activity [177], and LH [181].

a hot flash only when that threshold falls below the individual's T_{core} [180]. The story becomes complicated more by the normal circadian variation in the thresholds for sweating and vasodilation. Several studies have shown that the threshold of either T_{core} or mean body temperature (a weighted combination of core and skin temperature; T_{body}) at which peripheral vasodilation or sweating occurs is higher in the

afternoon/evening (when T_{core} normally peaks) than it is in the morning (when T_{core} is lowest) [183–186]. Those studies were conducted predominantly with males, but with enough female participants to suggest that the scenario is the same in the two sexes. The changes in thresholds across the day are thought to arise via input to the thermoregulatory centers in the hypothalamus from the nearby suprachiasmatic nucleus, where the master-clock drives the circadian rhythm in most physiological systems [187,188]. That input results in dynamic variation in the thresholds for thermoregulatory effectors across the day, and results in the normal daily rhythm of T_{core}. Thus, the normal daily operation of the POA involves shifting thresholds for thermoregulatory effectors, raising the possibility that threshold shifts in symptomatic menopausal women might involve the circadian system.

It was mentioned above that active vasodilation and sweating both involve the sympathetic cholinergic system. In support of the possible involvement of the sympathetic nervous system in hot flashes, Low and colleagues found a four-fold increase in efferent skin sympathetic nerve activity before and during a hot flash, which returned to baseline after a hot flash and was accompanied by an increase in sweat rate and cutaneous vascular conductance [177]. Freedman and colleagues [189] showed that yohimbine (an alpha-2 adrenergic antagonist that increases brain norepinephrine levels) provoked a hot flash, and that clonidine (an alpha-2 adrenergic agonist that reduces brain norepinephrine) ameliorated them, leading them to hypothesize that elevated levels of norepinephrine in the brain could narrow the inter-threshold zone in symptomatic individuals [18,190], or could be a separate or related trigger for hot flashes [182]. Why or how a decrease in feedback from sex steroids, or other change that occurs during menopause, might lead to an increase in norepinephrine in the brain remains unclear [190,191]. Further work is needed to examine the possible thermoregulatory and non-thermoregulatory triggers of menopausal hot flashes.

Monitoring hot flashes

Several tools and methods have been used to assess hot flashes and night sweats in the context of clinical trials and research [192]. Assessment tools include questionnaires that rely on retrospective recall of symptoms over a certain period, such as the past week, as well as daily diaries and event markers that participants can use to report or identify the daily occurrence and intensity of their symptoms. Scales typically assess symptom frequency (e.g. number of hot flashes per day) and severity (e.g. mild, moderate, severe), although the subjectivity of the measurement can be influenced by mood and expectations [193]. Daily symptom diaries yield detailed data with minimal risk of recall bias, however, they can be burdensome to participants [192]. Also, hot flashes that occur during sleep may be under-reported retrospectively in the morning [194,195].

A limited number of research laboratory and short-term ambulatory studies have investigated the use of objective measurement of hot flashes. A hot flash can be objectively identified by a sudden increase in sternal skin conductivity associated with increased sweating, which tails off as sweating decreases, measured by passing a small current (0.5 V) across electrodes containing a hydrophilic gel attached to the sternum; this method is considered the gold-standard method of measuring the frequency of hot flashes [22,194,196–201]. Based on a systematic review, sternal skin conductance has adequate sensitivity (0.69, proportion of hot flashes identified by a rise in sternal skin conductance that were accompanied by self-report) and specificity (0.97, proportion of times the skin conductance measure did not meet the criteria for a hot flash when a hot flash was also not self-reported) for detecting hot flashes, at least in laboratory conditions [202]. Factors like body mass index, negative mood, and stress can influence the concordance between hot flashes identified from self-reports and sternal skin conductance [201,203]. Also, the amplitude of the skin conductance does not represent the self-reported severity of a hot flash [193]. The most widely accepted rule for the detection of a hot flash is based on an observed rapid rise of at least 2 microSiemens in sternal skin conductance within a 30-second period [22,194,197,198]. More advanced techniques have been explored to improve the detection of hot flashes automatically from recordings of skin conductance, using pattern recognition techniques like support vector

machines, neural networks, and template matching [196,200,201], however, these techniques are mostly in the development phase and have not been applied to track hot flashes in clinical trials. Research is also ongoing to develop algorithms that can detect the onset of hot flashes based on a rise in skin conductance [204] or other characteristics of the physiological hot flash that reflect the thermoregulatory response [205]. As skin conductance sensors become more widely implemented in commercial devices, there is the potential for hot flashes to be tracked over longer periods of time with relatively low burden to users.

Hot flashes across the day and during sleep

In a study on the diurnal rhythm of hot flashes, based on 24-hour ambulatory recordings of sternal skin conductance and body temperature (ingested telemetry pill) in a sample of 10 women, the frequency of hot flashes peaked in the evening (at ~ 18:25 h, on average), which is when T_{core} is highest [24] (Figure 4). However, in another study with a much larger sample of 42 peri- and post-menopausal individuals who completed two days of ambulatory monitoring of sternal skin conductance, hot flashes were more likely in the late morning/early afternoon (10:00–-14:00 h) and late afternoon/early evening (14:00–-18:00 h) than in the later evening (18:00–22:00 h). On average, each participant had more frequent hot flashes during the waking hours (8.8 ± 5.6, range: 1–25; hot flash detected ~every 1.5 hours) than during the sleeping hours (3.7 ± 2.2, range: 0–8; hot flash detected ~every 2.6 hours) [203]. To our knowledge, no study has examined whether there is a relationship between the frequency of hot flashes and ultradian increases which occur every 2-5 h in T_{core} [179,206,207]. The normal aperiodic cycling of T_{core} may be associated with increases in T_{core} that are sufficient to exceed the threshold for sweating in symptomatic individuals, if indeed this is necessary for a hot flash to occur.

Hot flashes that occur during sleep appear to have the same physiology as hot flashes that occur during the daytime [40]. However, they can be considered separately from hot flashes during wake because of additional factors that need to be considered, including the disruptive effect that they have on sleep. Several studies have relied on self-reported measures showed that nocturnal hot flashes are associated with poorer sleep quality and insomnia (reviewed in detail in [208,209]). The strong link between hot flashes and sleep disturbance is further supported by studies showing that the treatment of hot flashes (see below) with hormone therapy reduces sleep disturbances [210–213]. Laboratory studies in which individual hot flash events have been objectively measured and related to polysomnographic (PSG) measures of sleep and wakefulness have had mixed findings. One study found that awakenings were more likely to occur before, than after, a hot flash [214], and another found that hot flashes occurred before an awakening only in the first half of the night [215], whereas others found that the majority of hot flashes coincide with awakenings [179,194,216,217] with no differences in the first and second part of the night [194]. One of those studies found that perimenopausal individuals ($n = 34$) had an average of 3.5 hot flashes per night and that 70% of hot flashes were associated with an arousal from sleep, with only a minority (20%) occurring without disturbance to sleep; the remaining hot flashes occurred when the participant had already been awake for at least one minute [179,194]. A subsequent study in a larger sample of 86 individuals also found that most of the detected hot flashes (51%) were associated with sleep disruption, and 29% of hot flashes occurred in undisturbed sleep; the remainder happened during wakefulness or were ambiguous (Figure 5) [179]. Possible reasons for the variability in findings between studies could be related to how hot flashes were defined in relation to sleep-wake epochs, sample size, or inter- and intra-individual differences in the extent to which hot flashes disrupt sleep. When considering the total impact of hot flashes on sleep, hot flash-associated wakefulness, defined with PSG, accounted for, on average, 27% of total time spent awake during the night, with large inter-individual variability [194]. Data from an experimental model of new-onset hot flashes in young pre-menopausal individuals, treated with a gonadotropin-releasing hormone agonist that simulates menopause, support a sleep-disruptive effect of hot flashes: individuals who developed hot flashes following treatment had a worsening of recorded sleep efficiency [219]. In a follow-up analysis, these authors showed that hot flashes occurred primarily in association with light (stage N1) sleep (20%) and wake epochs (51%), and that the majority of hot flashes (80%) occurred before or concurrently with an awakening,

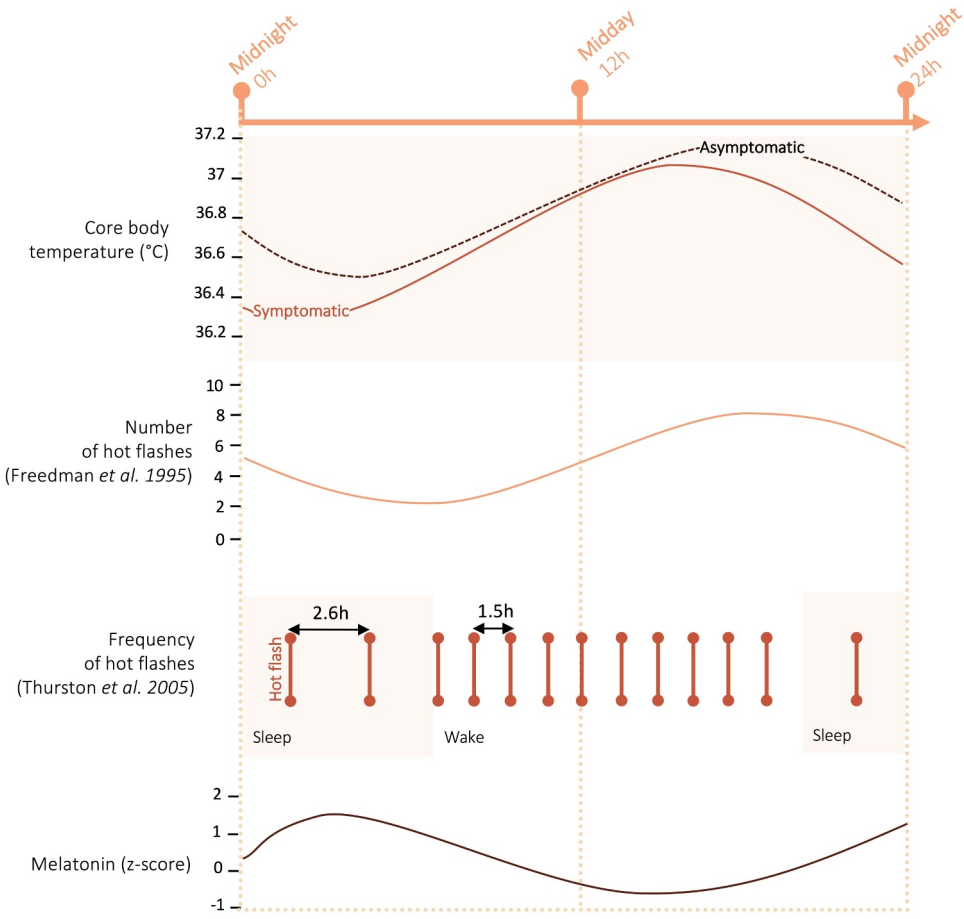

Figure 4. Schematic figure of the changes over the course of a day, in T_{core} in symptomatic and asymptomatic individuals, and number of hot flashes reported by Freedman et al., in 1995 [24], as well as the average frequency of hot flashes across day and night periods reported by Thurston et al., in 2005 [203], and distribution of melatonin levels across 24-hours [218]. In both studies, hot flashes were detected from sternal skin conductance monitoring.

with a similar pattern in both halves of the night [220]. Taken together, these findings show that nocturnal hot flashes are a significant source of sleep disruption.

Hot flashes may themselves trigger arousal from sleep but the strong overlap in timing between many (but not all) hot flash events and awakenings could also reflect a common mechanism within the central nervous system in response to estrogen withdrawal [221], involving central sympathetic activation or the KNDy neuron network. As mentioned above, the KNDy neurons that project from the ARC to neurons in the MnPO, are likely involved in thermoregulation, but given the importance of the MnPO for sleep [222], those projections could also influence sleep. KNDy neurons also project densely to the sub- paraventricular nucleus of the hypothalamus and the dorsomedial hypothalamus in the brain, both of which are implicated in the modulation of the circadian rhythms of sleep and temperature [223,224]. Further work is needed to determine if changes in the KNDy neurons that occur with the approach to menopause directly alter sleep-wake regulation independently of hot flashes.

In the context of sleep, it is important to consider sleep stages because the physiology of rapid eye movement (REM) and non-REM sleep are quite different. Experimental studies have shown that hot flashes are less likely in REM than in non-REM sleep [179,194,215], possibly due to the lower sensitivity of the thermoregulatory system, and an associated decrease in sweating responses, during REM sleep [225]. Hot flashes that occur in REM sleep are also less likely to be associated with an

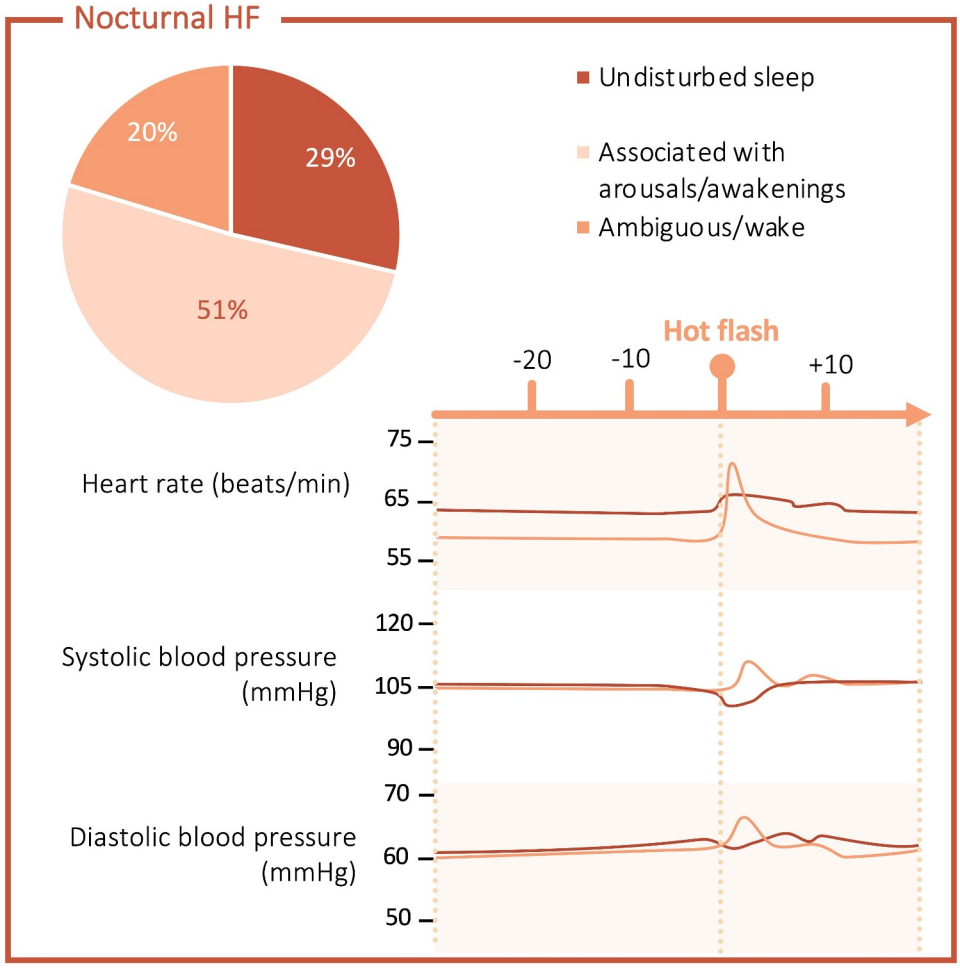

Figure 5. Physiological changes that occur across a nocturnal hot flash. This figure is based on the results of a study that examined changes in heart rate and blood pressure across hot flashes that occurred during undisturbed sleep (dark line) and hot flashes that were associated with an awakening or an arousal (light line) [179]. Eighty-six individuals contributed 542 hot flashes for analysis of heart rate and 45 individuals contributed 261 hot flashes for the analysis of blood pressure. Hot flashes associated with arousal/awakening were accompanied by an increase in both systolic and diastolic blood pressure and an increase in heart rate. Hot flashes that occurred in undisturbed sleep were accompanied by a drop in systolic blood pressure and an increase in heart rate, which was of smaller magnitude than that for a hot flash associated with an arousal.

arousal [179]. Possibly, when hot flashes do occur in REM sleep, they are less intense than in other sleep stages, and therefore less likely to be associated with an awakening, although this hypothesis remains to be tested.

Aging vs menopause and effects on thermoregulation

In most individuals, menopause occurs during a life period when other signs of aging start to manifest, which could affect the thermoregulatory system independently from any effect of menopause. However, with aging, several mechanisms ensure that the thermoregulatory system is flexible enough to adapt to thermal challenges [226,227].

Studies of the effect of aging on temperature-sensitive nerve endings, ascending fibers, and primary cortical projections, have not identified any alterations, so it is hypothesized that aging may rather cause structural changes that affect the thermal conductivity of the skin, or that decreased skin vascularization may alter the functionality of temperature receptors [227]. While many of the effects of aging on thermoregulation are apparent in the elderly, there are some changes that occur

gradually across the lifespan and may be evident in midlife when menopause occurs. For example, the temperature interval that is necessary to trigger a change in temperature sensation increases linearly through the lifespan, from about 1°C at around 10 years old to 4°C at around 70 years old [228]. On average, the sensitivity and capacity to adjust to a thermal challenge decreases gradually with aging, leading to a wider inter-threshold zone. Therefore, a proportion of individuals who are in the menopausal transition may already have significant effects of aging on their thermoregulatory system, while for some others, the effects of aging on thermoregulation may be small.

Whether there are differences in thermal comfort in relation to menopause has not been extensively investigated. A controlled experimental study compared the T_a thresholds for warm thermal unacceptability, warm thermal discomfort, and a preference for a cooler environment in 15 premenopausal and 23 postmenopausal individuals while they completed up to three trials at different metabolic rates throughout a protocol that ramped up T_a (increase of 1°C every 20 min) [229]. The investigators purposefully chose a narrow age range for all participants (40–60 years) to minimize age-related effects between the groups and controlled for any effect of hot flashes that might have occurred during the experimental sessions (hot flashes were experienced by 65% of postmenopausal participants during the sessions). They found a significantly lower T_a threshold for thermal unacceptability (pre-menopausal: 29.6 ± 2.5°C; postmenopausal: 28.7 ± 2.2 °C) and a prefe rence for cooler conditions (by ~ 1°C) in postmenopausal compared to premenopausal individuals, although there was no difference in the T_a threshold for warm thermal discomfort [229]. These data suggest that there may be changes in the thermoregulatory system occurring around menopause beyond the experience of hot flashes.

In our laboratory, we recently found evidence of altered profiles of T_{skin}, as measured overnight with a wearable device on the finger (Oura ring), in midlife individuals who were either in the late reproductive stage or in the menopausal transition ($n = 40$, mean age ± SD 46.6 ± 2.8 years) compared to young individuals ($n = 56$, mean age ± SD 25.6 ± 5.5 years). This difference also appeared to be independent of hot flashes since a minority (20%) of individuals in the menopausal transition reported hot flashes. Based on analysis of temperature curves fitted to nightly averaged T_{skin} measures collected across an ovulatory menstrual cycle, midlife individuals had, on average, a higher mesor of the finger temperature curve, but no difference in the amplitude of the curve (from a minimum in the follicular phase to a maximum in the luteal phase) across the menstrual cycle, compared to young participants [230]. It is possible that the higher mesor T_{skin} of the finger in midlife individuals could reflect enhanced peripheral vasodilation in those individuals. in that case, it would be expected that they would have a lower T_{core} if other factors, such as metabolic rate, remained the same. While T_{core} was not measured in that study, others have reported that T_{core} is lower in postmenopausal than in premenopausal females [231], which suggests that there is a shift in temperature regulation during this stage. More studies are needed to investigate whether an increase in T_{skin} temperature measured in the finger at night is linked to aging of the thermoregulatory system, to the onset of menopause-associated hormonal changes, or to both.

Effects of environmental temperature on hot flashes

Several studies have suggested that the environmental temperature can have an influence on the occurrence of hot flashes, although patterns are not clear. In a laboratory study, when T_a was set to a cool (19°C) compared to a warm (31°C) level, a reduction was measured in the frequency of hot flashes (3.0 hFs/8 h vs 12.2 hFs/8 h, $p < 0.001$) their intensity (2.0 vs 5.6, $p < 0.007$), and duration (2.1 min vs 5.5 min, $p < 0.054$) [232]. The lowering of bedroom temperature to 18°C reduced the number of hot flashes in the first half, but not the second half, of the night in post-menopausal individuals, and reduced awakenings overall [215]. Anecdotally, individuals report that application of something cold to the skin or being in a cold environment, provides relief [233,234]. Recent limited work, including our own, suggests that peripheral skin cooling can reduce interference from nocturnal hot flashes and improve perceived sleep [235–237], although it is not clear if this

effect is due to suppression of hot flashes or if hot flashes still occur but have less impact. It should be noted that the range of temperature corresponding to the thermal comfort zone is narrower than the TNZ, which may imply that animals including humans may adopt behaviors to seek thermal comfort even before reaching the margins of the TNZ [238]. Despite the apparent normality of cold-seeking behaviors including use of fans, removing layers of clothes, contact with cold objects or relocation to colder environments, the studies on these behaviors in the context of menopause are scarce and require more scientific attention.

If environmental temperature does influence the occurrence of hot flashes, then one would expect to see differences with season. In the USA, the SWAN found that hot flashes were more common in summer (July) than in winter (January). Similarly, the highest frequency of night sweats was in June, and the lowest in December [43]. In another study, based in the United States, some but not all individuals reported a seasonal variation in hot flashes, with worse symptoms in the summer [234].

Several works have compared reports of hot flashes between different countries, all relying on self-reports of hot flashes. Within a country, biases that could influence results from self-reporting will likely have a smaller effect than when countries with different cultures are compared. Factors such as cultural and language differences can influence the characterization of a hot flash, and the environment could too, as a hot flash may be less obvious in a very humid and warm environment. Sievert and Flanagan (2005) hypothesized that individuals developed climate-specific thermoneutral zones according to their location, and integrated 54 studies on the frequency of hot flashes from diverse countries [239]. In countries that had a larger range of T_a across the year due to greater seasonal temperature changes, participants were more likely to report that they experienced hot flashes than were the ones in countries that had smaller temperature fluctuations across the year. Surprisingly, individuals living at lower latitudes, where there was little difference between the hottest and coldest months, and a higher mean annual T_a, reported fewer hot flashes [239]. The authors interpreted these findings as possibly an acclimatation to T_a, suggesting that the coldest month, or the seasonal change, might apply a thermal stress to which the thermoregulatory system adapts, such that the TNZ is narrower in those individuals who live in colder or more variable climates, compared to those who are accustomed to warmer climates, or that those individuals who live with more seasonal variability may be more sensitive to temperature variations [239]. In contrast, another study that compared self-reports of hot flashes in 896 peri- and post-menopausal individuals from Chile, Ecuador, Panama, and Spain, found that those who lived in climates with higher T_a and lower altitudes were more likely to report more frequent and severe hot flashes [240]. Two other studies, one that compared individuals living in diverse climates within the United Arab Emirates and the other from India, did not find any significant associations between climate (T_a or seasonal variation) and the prevalence of hot flashes [43,241,242]. As mentioned above, cultural and language biases, or the environment itself, could have contributed to the discrepancies encountered between these studies. In addition, these studies reflect a snapshot in time and do not rigorously distinguish adaptation of the thermoregulatory system to years under a certain climate from the effects of acute exposure to particular environmental conditions. Finally, seasonality was mainly characterized as the annual amplitude of variation in the T_a, while in some places the seasonality is more marked by extensive changes in humidity, which could also affect the experience and reporting of hot flashes.

Climate change

The lack of a clear relationship between climate and the occurrence of hot flashes means that it is difficult to predict how climate change will affect thermoregulation in menopausal individuals. The key feature of climate change in most regions is an increase in T_a, together with an increasing frequency and duration of heat waves [243]. Higher $T_a$may not only have a direct effect on thermoregulation, but also indirect effects, for example, by

influencing psychological wellbeing and disturbing sleep [244]. Higher nighttime temperatures, associated with climate change, may disrupt sleep directly [245] as well as indirectly if the higher temperatures do lead to a an increased occurrence of hot flashes and associated awakenings. The possible effects of climate change on menopausal hot flashes is only just being considered, as highlighted in a recent commentary, which recommends a need for intersectional research that accounts for the multilayered facets that influence the impacts of climate change on human health [246].

Effects of exercise on hot flashes

Our knowledge on the relationship between menopausal hot flashes and exercise is limited, and the literature is mixed, influenced by several factors, such as the duration, type, and intensity of exercise that was examined. Exercise training is known to trigger numerous physiological adaptations [247], including an improved work capacity, decreased heart rate, increased metabolic rate, increased maximal oxygen consumption, and improved ventilation through its effects on the cardiovascular and respiratory systems. It also reinforces the musculoskeletal structure increasing bone density, and the muscle tone, volume, and strength. Of the numerous physiological mechanisms that are affected, several are likely to counteract the effect of aging on the thermoregulatory system and could influence thermoregulation in females across the stages of menopause. By regularly activating heat loss effectors, exercise can alter the threshold (begin to sweat at a lower T_{core}) and sensitivity (slope of the response between T_{core} and sweating) of the sweat response to an increase in T_{core}, leading to more robust heat loss responses. Because aging in general leads to a decrease in autonomic responses such as sweating, regular exercise could slow the effects of aging [227,248,249]. Through its effect on muscle, metabolism, and energy intake, exercise may also maintain a greater capacity to endogenously generate heat as muscles would conserve a relatively higher capacity for shivering and a higher basal metabolism [247]. Through these influences on the thermoregulatory system regular exercise may attenuate the onset and intensity of hot flashes.

Several studies have reported that regular exercise training leads to a lower frequency and intensity of self-reported hot flashes, however, some randomized controlled trials, even with a one-year long intervention, have failed to find an effect [248–250]. A 2014 meta-analysis that reviewed randomized controlled trials qualified the available evidence as “low quality” [250]. Subsequently, however, it was shown that exercise training for 16 weeks led to a lower self-reported severity of hot flashes accompanied by within-flash changes in cutaneous vasodilatation, sweating, and cerebral blood flow and improved thermoregulatory control [251]. A more recent meta-analysis appraised 21 randomized controlled trials involving 2,884 participants, and found that exercise lessened the severity of vasomotor symptoms, but with low certainty of evidence, while there was no difference in the frequency of vasomotor symptoms between subjects in the control and exercise groups, with high certainty of evidence [252]. Resistance training (for 15 weeks), assessed in only one study, led to a 44% decrease in the frequency of moderate and severe hot flashes [253]. The type and intensity of exercise, as well as duration of training programs and the effects on the thermoregulatory system, is likely to affect the experience of hot flashes [248,250] Heterogeneity of studies, small sample sizes, and the reliance on subjective measures of hot flashes makes it difficult to tease out the effects of exercise on vasomotor symptoms [252]. In addition, most studies do not take the stage of menopause into consideration or account for the sociodemographic background of the participants [248,250] Exercise may well lead to improvements in the subjective experience of hot flashes, such as through improvements in mood and wellbeing, rather than through a reduction in the symptoms themselves.

While studies have considered exercise training as a lifestyle intervention protective against hot

flashes, it is also plausible that exercise itself could be an acute trigger for hot flashes: the effect of exercise on the threshold for sweating works in the same direction as does menopause in symptomatic individuals, that is, it lowers the threshold for sweating and thus would make a hot flash more likely. Freedman and Krell reported that a laboratory exercise session at 40% predicted maximum oxygen consumption triggered a hot flash in all 12 individuals who were symptomatic for hot flashes [23]. In a larger sample of 42 individuals who reported daily hot flashes, Thurston and colleagues found that objective hot flashes were more likely within 30 minutes after self-reported physical exertion or after high physical effort; in contrast, regular aerobic exercise was associated with a slightly lower rate of objective hot flashes, indicating the importance of distinguishing effects of acute bouts of exercise versus habitual exercise [203]. Other studies, however, found either no relationship between acute measures of physical activity and hot flashes, or that acute exercise decreased hot flashes (see [248] for review).

In summary, more research is needed to clarify the relationship between exercise and hot flashes. In particular, more work is needed to determine whether exercise training, accompanied by training-related adaptations to the thermoregulatory system, ameliorates either the experience and severity of hot flashes or the objective frequency of hot flashes, and whether particular types and intensity of exercise training have a positive influence on the thermoregulatory system and in particular the mechanisms involved in triggering hot flashes.

Body composition and hot flashes

Much as with the effect of regular exercise, studies on the associations between the body mass index (BMI) and hot flashes have reported conflicting results. For instance, a 5-year cohort study on 631 individuals found no association between hot flashes and BMI, nor with the evolution of BMI across the years of study [254]. A meta-analysis that integrated data from 4,219 individuals identified a small increase in risk for hot flashes in overweight (BMI $>25\,kg.m^{-2}$) and obese (BMI $>30\,kg.m^{-2}$) individuals [255]. In terms of the link between hot flashes and lean mass, one study found that a higher lean mass was associated with fewer vasomotor symptoms [256] and another found that trunk lean mass was a protective factor against moderate to severe hot flashes [257]. An early hypothesis was that obesity could be protective against hot flashes and their severity, because adipose tissue produces the enzyme cytochrome P450 aromatase, which converts androgens to estrogens [258,259]. However, the finding that more fat mass is associated with greater likelihood of more severe hot flashes gave rise to a second hypothesis, namely that excessive fat mass may interfere with the capacity of the body to dissipate heat in an efficient manner, hence affecting the thermoregulatory system and favoring hot flashes [258,259]. The finding that subcutaneous, but not visceral, adiposity is associated with the risk of hot flashes supports that second theory of a mechanical barrier to heat dissipation [260]. It is also possible that endocrine function of the adipose tissue could influence thermoregulation, as some associations have been found between adipokine levels and hot flashes [258,259,261]. For example, higher levels of leptin and lower levels of adiponectin have been measured in postmenopausal symptomatic than asymptomatic individuals [262]. These effects of adiposity on hot flashes may also vary according to the stage of the menopause transition [259,261], although more studies are needed to confirm this idea. An association between body adiposity and hot flashes led to the hypothesis that diet changes and weight loss might lead to a reduction in hot flashes. This hypothesis was tested in a large trial of more than 17,000 postmenopausal individuals by investigating the effects of a dietary intervention designed to reduce fat intake and increase intake of fruit, vegetables, and whole grains, and lead to weight loss compared to a control condition [263]. After one year, individuals in the dietary intervention group who also lost weight were more likely to have eliminated vasomotor

symptoms than individuals in the control group who maintained their weight, with pronounced effects in those who originally had mild symptoms.

Recently, investigators have used longitudinal SWAN data to examine whether there is evidence of the reverse relationship between vasomotor symptoms and weight gain [264]. They found that increases in vasomotor symptoms, onset of high frequency symptoms, and cumulative exposure to vasomotor symptoms over time were associated with weight gain. Specifically, cumulative exposure to a high frequency of vasomotor symptoms (≥6 days in a 2-week period) over 10 consecutive annual visits was associated with increases in weight measures, including a 3.0-cm increase in waist circumference. Sleep problems partially (27%) mediated the relationship between vasomotor symptoms and waist circumference. Taken together, these studies suggest a bidirectional and multifactorial relationship between body composition and menopausal hot flashes.

Surgical menopause and cancer treatments

Surgical menopause occurs if a patient has both ovaries removed (with or without concurrent hysterectomy) prior to natural menopause. Patients who undergo bilateral oophorectomy are at increased risk for more severe hot flashes than are individuals in natural menopause [34], likely because they experience a rapid decline in the levels of estradiol and other ovarian hormones [265]. These individuals also exhibit a higher rate of mood disorders, sleep disturbance, sexual dysfunction, reduced quality of life, and an increased risk of long-term adverse health outcomes associated with early estrogen deprivation [265]. The North American Menopause Society recommends that, in the absence of contraindications, menopausal hormone therapy (MHT) for individuals with surgical menopause be continued at least until the average age of menopause (52 years) to treat hot flashes as well as to provide benefits for other aspects of health [266].

Individuals who undergo treatment for malignancy frequently experience menopausal symptoms as a side-effect. Tamoxifen is a selective estrogen receptor modulator that blocks the effects of estrogen on cancer cells. The drug also causes changes in the circulating level of FSH and estradiol [33]. Eighty percent of the premenopausal individuals who are prescribed tamoxifen develop vasomotor symptoms [267], with 60% reporting severe symptoms [268]. In survivors of breast cancer, nocturnal hot flashes are specifically associated with poor sleep [269,270] and PSG-defined sleep disturbance [271]. Since antiestrogen therapies like tamoxifen are prescribed for five to ten years, symptoms can be chronic, and effective management is required [267]. Menopausal hormone therapy is contraindicated in individuals with, or at high risk for, breast cancer, and therefore other options should be considered. Selective serotonin reuptake inhibitors (SSRIs) reduce hot flashes, however, the coadministration of some SSRIs, including paroxetine and fluoxetine, which significantly inhibit the CYP2D6 enzyme that converts tamoxifen to its most active metabolite, endoxifen, should be avoided in breast cancer survivors [272]. Venlafaxine does not interact with tamoxifen and seems to be a preferred choice in survivors of breast cancer who take tamoxifen [273]. Non-pharmacological approaches, such as cognitive behavioral therapy, are also an option in survivors of breast cancer [267]. Cognitive behavioral therapy leads to improvements in problem ratings of vasomotor symptoms in survivors of breast cancer as well as in menopausal individuals [268,272].

Treatment of hot flashes

In about 25% of menopausal individuals, hot flashes are severe enough to require treatment [274]. There is a growing number of options for the treatment of severe hot flashes and night sweats, which are briefly described here. The reader is referred to other papers for a more comprehensive review of treatment options, including the 2022 North American Menopause Society's position statements on hormone therapy [275] and non-hormonal options for hot flashes [272] as well several reviews [15,35,276].

MHT is FDA-approved as a first-line therapy for the relief of moderate to severe menopausal vasomotor symptoms [275]. MHT refers to estrogen plus progestogen therapy in individuals who have an intact uterus, or estrogen alone in those

who have undergone hysterectomy. The progestogen protects the endometrium against chronic unopposed estrogen. The lowest effective dose of systemic estrogen therapy that provides benefits while also minimizing risks for the individual is recommended [275]. The safety profile of MHT is most favorable when it is initiated in individuals who are free of contraindications and who are younger than 60 years old or within 10 years of menopause onset [275].

There are multiple formulations, doses, and routes of administration for MHT, which have comparable high efficacy for relieving vasomotor symptoms, thus therapy can be personalized [275]. The onset of efficacy for MHT is two to three weeks with efficacy continuing to improve thereafter [277]. Compounded preparations of bioidentical hormones are not approved by the FDA and should be avoided [15,275,277].

In placebo controlled, randomized trials, MHT has been shown to reduce the frequency and severity of hot flashes, for example, reducing the frequency of symptoms by 75%. MHT has additional benefits including improvements in mood, sleep, and the prevention of bone loss [275]. However, it is estimated that worldwide only 10% of postmenopausal individuals use MHT [278]. There are multiple reasons why postmenopausal individuals do not use MHT, including persistent concerns about safety following the findings of the 2002 Women's Health Initiative trials. Overall, the increased absolute risk associated with estrogen plus progestogen therapy or estrogen therapy is small (<10/10,000/y) [275]. Other reasons for low MHT usage include contraindications to using MHT, for example a history of breast cancer, heart disease, or stroke [279]. Based on a 2021 global survey of postmenopausal individuals with vasomotor symptoms, MHT was contraindicated for about one in ten individuals [280]. Also, 54% of women in the USA indicated that they did not want to use MHT despite being potentially eligible [280]. Many postmenopausal individuals (50–75%) use complementary and alternative approaches including lifestyle changes, mindfulness-based interventions, acupuncture, and supplements such as black cohosh and soy isoflavones to manage their menopausal symptoms [276], despite limited or mixed evidence for the efficacy of those approaches [272]. Given the high preference for non-pharmacological treatment, there is clearly a need for more rigorous randomized clinical trials to evaluate the efficacy of some of these complementary and alternative approaches. It is essential for trials to be controlled with a rigorous placebo or active control for behavioral interventions, given that there is a significant placebo response for reported hot flashes [15].

Other than those complementary and alternative approaches, non-hormonal options for vasomotor symptoms include serotonin norepinephrine reuptake inhibitors or SSRIs and gabapentin [272]. Low-dose paroxetine has been approved by the FDA to treat vasomotor symptoms, although paroxetine and venlafaxine have similar efficacy, reducing vasomotor symptoms by 40% to 65% [15].

Novel nonhormonal treatments for vasomotor symptoms that directly target the mechanism of hot flashes involving the KNDy neuron complex (See [172]; [278] for reviews) are becoming available or are under development. As commented by Christ and colleagues [172], these targeted therapies came about only after the basic science, mostly by Dr. Rance and colleagues over a period of several years, led to an understanding of the underlying mechanisms of hot flashes [137]. That knowledge guided the development of a new class of medications. In May 2023 the FDA approved fezolinetant (45 mg), a selective NK_3R antagonist for the primary indication of treatment of menopausal vasomotor symptoms [278]. As mentioned in the above sections, NKB has a high affinity for NK_3R receptors in the thermoregulatory center of the POA, and those receptors are blocked under fezolinetant treatment, decreasing the activity of heat defense pathways and leading to reduced frequency of hot flashes [281]. The Phase 3 clinical trial found that compared with placebo, fezolinetant significantly reduced the frequency and severity of vasomotor symptoms at week 4 and week 12 (~61% [32.7] mean change from baseline), with improvements observed after one week and maintained over 52 weeks [281]. There was no significant improvement in patient-reported sleep

disturbance at week 12 (secondary endpoint), although fewer participants had severe sleep problems with fezolinetant than with placebo [281]. Importantly, serious adverse events were infrequent and abnormalities in liver function were rare and transient. Another neurokinin (NK) receptor antagonist, that recently underwent Phase 3 trials, is elinzanetant, an antagonist of both the NK_1 and the NK_3 receptors [282]. This dual antagonism is hypothesized to treat

Table 1. Research agenda: current gaps in the knowledge on the effect of menopause on the thermoregulatory system.

Aim for a personalized approach	Across the literature reviewed, there is good evidence of inter-individual variability in the severity, frequency, and duration of hot flashes, as well as in the physiological characterization of hot flashes. For example, not all individuals show increased T_{core} in the 30-min before a hot flash, and not all post-menopausal individuals develop hot flashes. There may also be inter- and intra-individual differences in sweating thresholds as they approach menopause. There is a need to move toward a precision medicine approach, aiming to characterize each individual's experience of hot flashes and their thermoneutral/inter-threshold zone and if/how it changes with menopause, to ultimately adapt treatments to the individual. A precision medicine approach could also be used to predict who will be asymptomatic or symptomatic for hot flashes and when hot flashes will abate, using a wealth of data, including demographic factors, genetics, hormone profiles, and thermoregulatory measures such as circadian and ultradian thresholds of body temperature.
Accounting for diversity	Our knowledge about the physiology of hot flashes is based mostly on studies that have had small sample sizes. More work is needed on larger samples of more diverse populations, considering the influence of reproductive staging (e.g. menopausal transition, post-menopause), early onset of menopause, rate of change over time in reproductive hormones like estradiol and FSH, and demographic factors like race and ethnicity and body composition.
Modeling inter-threshold zone	More work is needed to investigate the physiological triggers of hot flashes such as whether the inter-threshold zone in individuals symptomatic for hot flashes narrows transiently due to a lowering of the UCT, and whether hot flashes tend to occur with the peaks of ultradian cycles of T_{body} superimposed on the circadian rhythm of T_{body}.
Measuring hot flashes objectively	Much of our knowledge about the relationship between hot flashes and health, and the effectiveness of treatments, has relied on self-reported measures of hot flashes. The perception and experience of hot flashes is vital for treatment-seeking behavior and to contextualize the effects of hot flashes of different severity on quality of life, however, there is a need for more studies to employ objective physiological measures of hot flashes (e.g. from skin conductance) in addition to self-reports to establish links between physiological hot flashes and health, and the effectiveness of treatments for hot flashes.
Validating an objective definition of hot flashes	To enable the collection of more data from more individuals during the transition to menopause, there is a need to advance the detection of objective hot flashes that can be paired with the tracking of other physiological measures. Validated measures need to be developed that can be applied in wearable and non-wearable devices. Also, more work is needed to identify a valid and objective measure of the intensity or severity of a hot flash.
Investigating effects of menopause on thermoregulation beyond hot flashes	The body of literature about thermoregulation in relation to menopause has focused mostly on hot flashes. More work is needed to understand whether there are other fundamental changes in thermoregulation that occur with changes in reproductive hormones across the menopausal transition that are potentially independent of chronological aging, and that could indicate sensitivity of an individual's thermoregulatory system to subsequent development of hot flashes.
Researching effects of KNDy neurons changes beyond hot flashes	An exciting development in the field of female's health has been the discovery of the role of KNDy neurons in the effects of changes in reproductive hormones on thermoregulatory centers in the brain, resulting in hot flashes. More work is needed to determine if these neurons also have a role in other physiological changes that occur across the menopausal transition, such as sleep disruption, which could, at least partially, occur independent of the disruptive effect of hot flashes.
Characterizing specific effects of progesterone changes in menopause	Progesterone has an important role in the menstrual cycle and the related variations of body temperature. However, in the context of menopause, further research is needed to understand whether the loss of progesterone cyclicity influences the changes in thermoregulation.
Understanding effects of history in a thermal environment on hot flashes	There are mixed data about the influence of climate and season on the experience of hot flashes, with most studies relying on self-reported assessments of hot flashes. Work is needed to determine how a lifetime of exposure to a particular climate (and the adaptation that will occur to that climate) influences the thermoneutral zone and/or the inter-threshold zone, and consequently the frequency and severity of hot flashes, in individuals. Such knowledge is particularly important given the warming and increase in frequency of extreme weather events associated with climate change.

vasomotor symptoms by acting centrally to reduce the activity of warm-sensitive pathways in the POA as well as acting peripherally (substance P/NK_1R antagonist action) by reducing peripheral vasodilatation [283]. NK_1 antagonists have been shown in other populations to reduce insomnia symptoms [284]. Preliminary evidence from phase 2 trials of elinzanetant provided evidence of improvements in sleep quality and reductions in awakenings from sleep [285] in addition to reductions in the frequency of vasomotor symptoms [283], which was supported in Phase 3 trials [282]. While these novel nonhormonal therapies for vasomotor symptoms represent a breakthrough by providing a targeted treatment option to individuals with severe menopausal hot flashes, more evidence in larger samples is needed in the future about their efficacy, whether they are effective and appropriate in individuals with contraindications for MHT, and whether drug efficacy is influenced by genetic characteristics of the population [278].

Conclusion

The hormonal changes that occur in the menopausal transition affect the thermoregulatory system, with the majority of individuals experiencing hot flashes as they approach menopause. These thermoregulatory events, while brief, can occur frequently across day and night and are disruptive to quality of life. Also, they persist across several years post-menopause in many individuals. Breakthroughs in basic science have recently been made in fundamental understanding of the underlying mechanistic pathways of hot flashes. In the presence of diminishing estradiol levels, KNDy neurons become hyperactive, which in turn sensitizes the heat defense pathway in the POA, triggering heat dissipation responses, i.e. hot flashes. One hypothesis is that under conditions of a narrower inter-threshold zone, normal ultradian variations of body temperature, combined with a lower threshold of body temperature for peripheral vasodilation and sweating, result in hot flashes, although not all findings are consistent with this hypothesis. It could also be that hot flashes result when the threshold for vasodilation and sweating falls below current body temperature, due to changes in the interaction between the circadian and thermoregulatory systems. Hot flashes may also result from a combination of all of those mechanisms. Arising from the discovery from basic scientists of the mechanistic role of KNDy neurons in hot flashes, novel treatments in the form of neurokinin B-antagonists are available and more are being developed, with the first clinical trials showing that they effectively decrease hot flashes. These treatments could potentially provide alternative treatment options to menopausal hormone therapy for disruptive hot flashes. Notably, important aspects of this topic remain to be fully understood, such as the influence of genetics, behavior, and environment on the frequency and severity of hot flashes. As highlighted in Table 1, several gaps in knowledge need to be addressed to provide a more complete understanding of the thermoregulatory changes that are associated with menopause.

Abbreviations

AMH	Anti-Müllerian hormone
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ARC	Infundibular (arcuate) nucleus
BMI	Body mass index
DYN	Dynorphin
ERα	Estrogen receptor alpha
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
GPR54	G-coupled protein receptor 54; a kisspeptin receptor
Kiss1R	Kisspeptin receptor
KNDy	Kisspeptin-neurokinin B-dynorphin
KOR	κ-opioid receptor
LH	Luteinizing hormone
MBH	Medial basal hypothalamus
MHT	Menopausal hormone therapy
MnPO	Median preoptic nucleus
NK	Neurokinin
NKB	Neurokinin-B neuropeptide: tachykinin
NK_3R	Neurokinin 3 receptor
POA	Preoptic area
PSG	Polysomnographic
REM	Rapid eye movement
SSRIs	Selective serotonin reuptake inhibitors
STRAW	Stages of Reproductive Aging Workshop
SWAN	Study of women across the nation
TACR3	Tachykinin receptor 3
T_a	Ambient (environmental) temperature
T_{body}	Mean body temperature (mean temperature of core and peripheral temperatures)
T_{core}	Core temperature
T_{skin}	Skin temperature
$T_{skin,tail}$	Tail skin temperature
TNZ	Thermoneutral zone

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