

# Hot flashes: why?

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## ABSTRACT

Hot flashes (HF), transitory episodes of erythema, heat sensation, anxiety followed by chills, are described in carcinoid syndrome, mastocytosis, medullary thyroid cancer, hyperthyroidism, pheochromocytoma, alcohol consumption, side effects of drugs, and infections. They are pivotal among menopause-related vasomotor symptoms beside genitourinary syndrome in addition to sleep disturbances (40-60% of females), and metabolic changes. HF affect 70% of women (20% of them have a severe impairment of life quality); they last for 4-7 years, starting 4-6 years before last menstruation. The main HF cause is ovarian-derivate estrogen deprivation which activates complex endocrine and neuroendocrine mechanisms involving noradrenaline, 5-hydroxytryptamine (5-HT), calcitonin gen-related peptide, orexin, kisspeptin, neurokinin B, and epigenetic elements like modulation of tachykinin receptor 3, accelerated epigenetic aging (as found in Women's Health Initiative Observational Study), expression of central serotonin transporters. Estrogen deficiency uncouples the negative feedback with preoptic area of hypothalamus, responsible for thermoregulation by inducing an exacerbated vasodilatory response to a small increase of body temperature. TRPV1 (transient receptor potential vanilloid 1) in preoptic hypothalamic area may play a role by NE- $\alpha$ 2ADR (norepinephrine-activated  $\alpha$ 2-adrenergic receptors) activation. Higher expression of serotonin transporter SLC6A4 causes a lack of 5-HT at synapsis which is a trigger for presynaptic 5-HT receptor feedback, thus a release of serotonin amount prevents hot flashes. Kisspeptin and neurokinin B which are co-expressed in infundibular nucleus of hypothalamus are involved in central thermoregulation and gonadotropin releasing hormone anomalies. The NK3R3 (neurokinin 3 receptor) antagonist receptor improves HF. Understanding the pivotal role of central neurotransmitters in hot flashes is the basis of new therapeutically researches because otherwise estrogen replacement has a long list of side effects, and it is contraindicated in breast cancer-related hypogonadism.

**Keywords:** hot flash, sweat, menopause, climacteric syndrome, vasomotor symptoms, estrogens, sleep, metabolic syndrome, serotonin, hypothalamus, thermoregulation, neurokinin B, norepinephrine

## INTRODUCTION

Hot flashes, transitory episodes of erythema (from 1 minute to 5 minutes) in association with a sensation of heat, anxiety followed by chills, are described in different systemic conditions like neuroendocrine neoplasia-related carcinoid syndrome, mastocytosis, disseminated medullary thyroid cancer, emotion flushing, hyperthyroidism, pheochromocytoma and paraganglioma, alcohol-related flush, side effects to different drugs,

food and beverages, infections etc. (1,2). Menopause, lack of menstrual cycle for 12 consecutive cycles because of ovarian function loss, is accompanied by vasomotor symptoms like hot flashes (also called “night sweats”, even they may also be presented during day time and many studies analyzed them separately), sleep anomalies, metabolic changes due to loss of ovarian estrogens production in addition to aging (3,4). Despite multiple animal models studies, several mechanisms are still incompletely known (3) (Figure 1).

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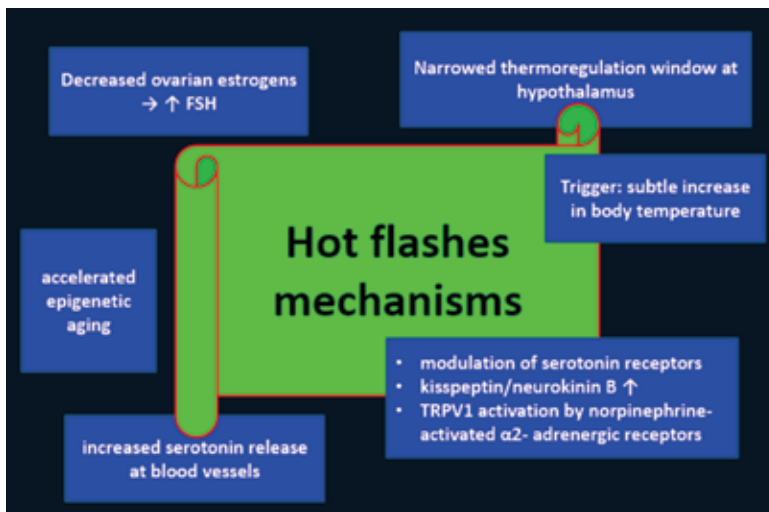
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**FIGURE 1.** Different mechanisms related to hot flashes (see abbreviations and references in text)

Progressive decrease of estrogens is essential in understanding the vasomotor symptoms, vulvovaginal atrophy, and genitourinary syndrome of menopause (5). New data suggested that epigenetic aging may be a contributor element to vasomotor symptoms with late onset, as provided by genomic data on Women's Health Initiative Observational Study (6). Prior genome-wide association studies revealed 20 loci related to ovarian aging (7). A meta-analysis from 2020 showed based on 18 studies that 14 variant genes (out of 26 gene candidates) like CYP1B1 (cytochrome P450) and tachykinin receptor 3 (TACR3) gene are related to vasomotor symptoms (8). TACR3 study was first published in 2017 in women between 50 and 79 years that were enrolled in Women's Health Initiative Study (9).

## AIM

We purpose a focus on mechanisms underlying hot flashes under menopausal conditions as major player in vasomotor symptoms constellation in addition to other anomalies.

## METHOD

This is a narrative review. PubMed data was used for research (50 references were cited).

## RESULTS

### Mechanisms of hot flashes

Peri-menopausal period of time, namely menopausal transition, which includes 4-6 years before the actually stopping of menstruation, is accompa-

nied by multiple symptoms and hot flashes represent the most frequent of them that may last for years (70% of females experience hot flashes, with an average period of time for 4-7 years) and may severely damage the quality of life in 10-20% of women (10). Their presence is a turning point in medical approach, mainly the estrogen substitution, which is required for 4-5 years (and even longer in some cases) to control hot flashes and vaginal atrophy, respecting the principle of the lowest efficient dose on shortest period of time, with progesterone association if uterus is present (11).

Hot flashes underline complex endocrine, epigenetic and neuroendocrine mechanisms; kisspeptin, neurokinin B, noradrenaline, 5-hydroxytryptamine (5-HT), calcitonin gen-related peptide are involved (12-14). Estrogen deficiency uncouple the negative feedback with hypothalamus; dysfunction of hypothalamic thermoregulation consists in a exacerbated vasodilatory response to a small increase of body temperature (a narrowed window of thermoregulation) (12,14). Hypothalamic regulation of body temperature affects preoptic area where different neurotransmitters and their receptors play a role in heat resumption (15). Recently, a murine experiment described TRPV1 (transient receptor potential vanilloid 1) in preoptic hypothalamic area with a role in hot flashes-related abnormal thermoregulation; TRPV1 being activated by NE- $\alpha$ 2ADR (norepinephrine-activated  $\alpha$ 2-adrenergic receptors), which are situated at the level of dorsal root ganglia (15). Other rodent studies showed a role of orexin in anxiety and thermoregulation (16). The neuropeptide is synthesized at the level of perifornical hypothalamus and it is inhibited by estrogen receptors, thus meno-

pause-related estrogen deprivation increases its central levels with consecutive exacerbation of hot flashes and anxiety (17). Moreover, murine models reproduce the skin temperature changes that mimic hot flushes in ovariectomized rats; recently, the idea that different areas of teguments differently respond to the ovarian status was suggested in these experiments (18). When it comes to central regulation of body temperature, serotonin also plays a role, including epigenetic regulation of serotonin transporters (19). For instance, higher expression of SLC6A4 (as revealed by microRNA studies) causes a serotonin lack at the level of synapsis which is a trigger for presynaptic 5-HT receptor feedback, thus a release of serotonin amount is present preventing the hot flashes (20). Severe phenotype of hot flashes is not correlated with cortisol and testosterone levels at the level of blood but with low estrogen, and increased FSH (follicle stimulant hormone) or decreased epinephrine/increased norepinephrine values; hypothalamic – pituitary – ovarian axes assays (estrogen/FSH) might serve as biomarkers of symptoms severity, as found in Seattle Midlife Women's Health Study (21). Vascular reactivity that causes the skin anomalies is related to adrenergic system (norepinephrine is more important than epinephrine) (22). But with respect to reducing the window of brain thermoregulation, estrogen/FSH are less important than central neurotransmitters like serotonin and epinephrine (23). During menopause transition, hypothalamus integrates both gonadotropin releasing hormones (GnRH) and thermoregulation *via* central neuropeptides like kisspeptin and neurokinin B, which are expressed in its neurons (infundibular nucleus) (24). In subjects with vasomotor symptoms, kisspeptin/neurokinin B are over-expressed opposite to dynorphin which is downregulated, while experimental administration of NK3R (neurokinin B receptor 3) agonists like senktide induces hot flashes, tachycardia, high skin temperature (25,26).

### Hot flashes – associated elements

Sleep anomalies accompany menopausal transition in 40-60% of females which is more frequent than during prior reproductive years, especially in women with general sleep disturbances, co-presence of anxiety and depression, familial pattern of having a certain cluster of sleep disturbances like insomnia, etc., phyco-social modulators (for instance, chronic alcohol consumption, marital/familial and professional dissatisfactions), and the presence of additional medical risk factors/condi-

tions like urinary anomalies, organic pain during the night influencing the sleep phases (as restless legs syndrome, joints, muscles and bones chronic pain, variations of blood pressure levels with associated headache during the presence of extreme high or low values) (27). A list of conditions that impair sleep during menopausal period of time include obesity, gastroesophageal reflux, different types of cancers, uncontrolled hyperthyroidism; also fibromyalgia has been reported to onset and aggravate during this period (28,29). “Domino hypothesis” has been suggested when describing the relationship between hot flashes and sleep anomalies, meaning that hot flashes aggravate the abnormal sleep while lack of adequate sleep decreases the threshold for hot flashes or may aggravate the depression (30). Moreover, hot flashes-related insomnia involves a constant hyperarousal, both before sleep time and all along during the day time (31).

Depending the severity of vasomotor symptoms, insomnia may be similarly treated as these symptoms (for instance, estrogens for subjects with severe hot flashes) or it may be approached based on cognitive behavioral therapy, antidepressants if depression is associated, paroxetine or oral melatonin (like prolonged-released formula with a good tolerance, being preferred in women over 55 years) (27). Therapy with transdermal estradiol and intermittent progesterone to control vasomotor symptoms showed that their improvement (including hot flashes and depressive elements) does not entirely control the sleep profile, probably because of the fact that some other mechanisms are actually involved during peri-menopause (32). On the other way, if sleep disturbances are not controlled, the mentioned associated diseases, which are potential additional factors to poor quality sleep, may aggravate; supplementary deterioration for cardiovascular status and obstructive sleep apnea syndrome have been suggested (33). Also, worsening of insulin resistance and onset of non-alcoholic fatty liver disease is described (34). Traditional explanation for increased cardiovascular risk in females with hot flashes is dysfunction of stress response under physiological conditions (35).

Another potential associated element of vasomotor symptoms is reduced memory capacity as reflected by executing a verbal memory task, probably due to estrogen deficiency-related effects on brain, mainly hippocampus and prefrontal cortex (36). Functional magnetic resonance imaging studies confirmed these aspects (37). Overall, sleep, mood and cognitive (so call “brain fog”) troubles have a major impact on quality of life (38).

Progressive estrogens deprivation may also cause hot-flashes accompanied metabolic dysfunctions like increased abdominal fat, dyslipidemia, arterial hypertension (39). One study from 2020 showed a statistically significant correlation between hot flashes and metabolic syndrome in women over 40 years (39). Weight control (meaning weight loss in females with increased body mass index) during menopausal transition might be a double hit for both controlling the hot flashes and metabolic anomalies, although hot flashes equally affect normal weighted women (40). For instance, Midlife Women's Health Study (a longitudinal trial between 2006 and 2015 that included 780 females, follow-up for 4-7 years, aged between 45 and 54 years) showed that body mass index is not correlated with hot flashes instead older age at menopause, peri-menopausal status, current smoker status, lower estrogens/progesterone values and co-presence of depressive symptoms are correlated with the presence of hot flashes (41). Other studies found that high frequency of hot flashes is correlated with endothelial dysfunction (42). A pool analysis published on 2021 included 18,555 females InterLACE (International collaboration on the Life course Approach to reproductive health and Chronic disease Events) data showed that early menarche age (prior to the age of 14 years) is associated with severe vasomotor symptoms (increased risk of both hot flashes and night sweats), but if the females were obese or overweighted during midlife in addition to early menarche, the menopausal symptoms are even more severe (43).

## DISCUSSIONS

Future medications are under development to address the central regulatory pathways against hot flashes, knowing that currently SSRI (selective serotonin reuptake inhibitors) are approved for vasomotor symptoms control especially in patients with contraindications to estrogens like survivals of mammary cancer (44,45). Antagonists of NK3R act at thermoregulation hypothalamic centrum to improve the pattern of vasomotor symptoms (44). Antagonists of neurokinin/NKR3 have proven clinical efficacy in both controlling the hot flashes and associated sleep anomalies (45,46). The improvement of GnRH levels under medication confirms the role of neurokinin 3 in menopause-associated symptoms while kisspeptin levels are not modified, probably because they are under direct influence of hypoestrogenic status (47,48). As an extension of kisspeptin (and its receptor Kiss-1) – neurokinin B complex signaling pathway, we mention the other end of the spectrum: their agonists used as ovulation inductors, for instance, in polycystic ovary syndrome or in controlling hypothalamic amenorrhea and delayed puberty (49,50).

## CONCLUSION

Understanding the pivotal role of central neurotransmitters in hot flashes is the basis of new therapeutically researches because estrogen replacement has a long list of side effects, and it is contraindicated in breast cancer-related hypogonadism.

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