What causes hot flushes? The neuroendocrine origin of vasomotor symptoms in the menopause

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Abstract
Vasomotor symptoms (VMS) such as hot flushes and night sweats are frequently encountered during menopause and can greatly reduce the quality of life. These symptoms are causally related to decreasing estradiol concentrations, mainly in the serum and subsequently also in the hypothalamic temperature regulating centre. The lack of estrogens alters neurotransmitter activity, especially in the serotonergic and noradrenergic pathways. Because sex steroids act as potent neuromodulators, the substitution of ovarian sex steroids by hormone replacement therapy is the most effective treatment option for VMS. When contraindications exist for the use of sex steroids, steroid-free drugs are a possible alternative. A better understanding of the physiology of thermoregulation, thermoregulatory dysfunction and adaptive processes of the brain may facilitate the development of new therapeutic approaches. Such drugs could then be used to treat vasomotor disorders even when the use of steroid hormones is contraindicated. This review article summarises our knowledge on the mechanisms of temperature regulation and describes deviations from this regulation during altered sex steroid conditions. Our current knowledge on neuroendocrinology of thermoregulation may serve as a basis for the use of steroid-free pharmacological intervention.

Keywords: Menopause, neuroendocrinology, temperature regulation, neurotransmitters, sex steroids

Introduction
Which doctor isn’t familiar with the complaints of menopausal women about severe sweating and hot flushes with reddening of the face? From a medical viewpoint, these complaints are usually treated by mere reassurance, because they often have only limited objective significance. However, if they are also accompanied by mood swings, depression or somatic complaints such as paroxysmal tachycardia, it is clear that vasomotor symptoms (VMS) associated with the menopause could also actually attain the character of a disease and could markedly reduce the quality of life. A therapeutic approach is then sought that addresses symptoms in a pragmatic way, but which probably ought to focus more effectively on the cause of these symptoms. The study of the underlying origin for the clinical manifestations of sex steroid deprivation is complex but fascinating; it provides insights into the intricate regulation of temperature and the complex reaction by interconnection of different organs. The aim of this review is to discuss some mechanisms for the cause of VMS in the menopause. Our knowledge on the generation of VMS may serve as a basis for development of some innovative therapeutic approaches for their treatment.

Epidemiology and symptoms
During the perimenopause, the majority of women experience recurrent symptoms such as hot flushes and night sweats [1]. Nearly one in every five women is so badly affected that they cannot tolerate these symptoms and seek treatment for them. In most women, VMS first occur years before the menopause and continue for five or more years after the onset. Even 10 years after menopause, about one in 10 postmenopausal women still suffer from hot flushes, although by this stage their number and intensity can vary considerably [1]. The severity of the symptoms differs widely, with large inter- and intra-individual variations [2].

Hot flushes usually last about 1-5 min, in exceptional cases even up to 15 min. Mild hot
flushes are experienced as a transient feeling of warmth; the more severe ones are characterised by a sudden heat that spreads over the upper body and face, and causes reddening of the skin and marked sweating.

A feeling of cold and shivering often follows the hot flush [3]. The latter are frequently associated with other non-specific vegetative symptoms such as feeling of pressure in the head or chest, agitation, nausea and tachycardia or tachypnoea. VMS include severe sweating during sleep (night sweats). This can disturb the night’s rest which can in turn lead to mood disorders, reduction in the quality of life and loss of energy and performance [3–19].

Hot flushes may be the first signs of fluctuations in serum levels of estrogens [16]. Symptoms generally occur in the late pre-menopause or perimenopause, i.e. from about the age of 50 years on. The start of VMS often precedes the last ovarian-controlled bleeding, a time-point which is generally considered to be the menopause [1,16]. The symptoms may be more severe in women with surgically induced menopause than in those with a natural, gradual loss of ovarian function [10].

In most women, the frequency and intensity of hot flushes and night sweats eventually decrease whereas postmenopausal years progress, but some women suffer from VMS all their lives [16]. One group of patients particularly affected by menopausal symptoms are those who, for therapeutic reasons, undergo a surgical or functional loss of ovarian function during their fertile years, or who receive anti-estrogen therapy. Men may also be affected by hot flushes after the loss of androgens [7,8,10]. Whether or not there is a direct connection between estrogen concentration and the intensity and frequency of hot flushes remains controversial [11,12]. There is a close temporal relationship between the occurrence of VMS and fluctuations in estrogen concentrations in the perimenopause and also with low levels after the menopause (Figure 1) [13–15].

Because the underlying mechanisms for the origin of steroid-deficiency symptoms are still not adequately understood, there are various hypotheses concerning the neuroendocrine genesis of vasomotor disturbances in the menopause. One current assumption is that VMS are caused by a derangement of the temperature-regulating circuit. This important regulatory mechanism consists of three major components: the CNS, the body core and the peripheral vascular system [14]. Disturbances in these thermo-regulatory centres cause deviations in temperature homeostasis.

The hot flush itself represents an excessive reflex response to an unphysiological stimulation of the heat centre consistent with a heat adaptation mechanism. Apparently, the body detects a change in temperature through dysregulation in the temperature centre. The system reacts to the feeling of overheating by peripheral vasodilatation, which in turn leads to sweating and then to compensatory cooling reaction [3,19]. Sometimes, marked heat loss even triggers shivering that supposedly compensates for the heat loss [15].

Figure 1. Representation of the relationship between serum estrogen concentrations and occurrence of vasomotor disturbances. During the reproductive phase, the menstrual cycle produces marked variations in hormone concentrations. In the perimenopause, these hormone levels alter in such a way that the regular cyclic variations are lost. The mid-cycle estradiol levels are no longer sufficient to trigger the pre-ovulatory LH peak. In this phase of falling estradiol concentrations, vasomotor disturbances occur that may also persist into the postmenopause.

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Thermoregulation and temperature thresholds

Thermoregulation is a complex biological system of neuroendocrine and autonomic structures that may maintain the core body temperature within the threshold values even when the surrounding temperature changes. In this way, thermoregulatory reactions such as sweating and shivering enable the body to keep its core temperature constant. This reaction is crucial for organ integrity and optimum function [14].

The thermoregulatory system controls core body temperature: it is balanced with a so-called upper set point for sweating and a lower limit for cooling. If the core body temperature goes below the lower set value, mechanisms to produce heat such as vasoconstriction or shivering are activated. If the upper threshold is exceeded, then the mechanisms for releasing heat such as vasodilatation and sweating are operative; excessive heat is lost through the skin by radiation and evaporation (Figure 2) [15,20].

These two thresholds, the sweating threshold with release of heat and the shivering threshold with heat conservation and renewed production, define the so-called thermoneutral zone [21]. This is maintained within specified limits that can vary rhythmically during the day [14,22]. Three correcting variables play an important role in this bidirectional control circuit:

- The body core with reporting of the body core temperature to the CNS via afferent thermosensitive signal pathways
- The CNS as the central switching point of the temperature parameters with efferent lines to the spinal column, brain stem, preoptic area, hypothalamus and limbic system
- The peripheral vascular system that receives efferent signals and transmits afferent signals to the CNS [23].

Temperature sensors of body core temperature are found, amongst other places, in the gastrointestinal tract, in intra-abdominal veins and in the spinal cord [24,25]. Thermosensitive nerve fibres in the skin as well as in the internal tissues are involved as triggers of thermoregulatory reactions [26]. Temperature information is processed within the CNS at several functional levels, but the hypothalamus, in particular the anterior hypothalamus with the preoptic area (POA), has pivotal importance in regulating this function [24,27]. The POA projects through the medial forebrain bundle into the brain stem and spinal cord [28]. Warm-sensitive neurones in the POA control the release of heat; effectors in the lateral hypothalamus, peri-aqueductal grey and in the reticular formation are responsible for peripheral vasodilatation and sweating [28–30].

The functionally coupled elements of the thermoregulatory control circuit are under catecholaminergic and/or serotonergic control. Serotonergic neurones of the dorsal raphe nucleus of the brain stem project into the POA. mRNA is also localised in pre- and postsynaptic serotonin receptors in the POA of primates [31,32]. Noradrenaline signal pathways likewise lead to the POA so that this area receives noradrenergic signals from the solitary nucleus and the locus coeruleus. Alpha-adrenoceptor mRNA has been detected in the POA and in the hypothalamus, and activation of β-adrenergic receptors also occurs in the same nuclear regions [33–35]. Vasomotor effectors, that control peripheral vasodilatation and vasoconstriction, are also modulated by noradrenergic and serotonergic signals [36,37].

Figure 2. Schematic representation of the regulation of core body temperature. Maintenance of core body temperature is crucial for organ integrity and optimum function [14]. Core body temperature is centrally regulated via an upper set point for sweating and a lower set point for cooling. In between, there is a thermoneutral zone in which the major thermoregulatory actions (sweating, cooling) are not induced [38]. (A) Normal temperature regulation with normal thermoneutral zone. (B) Thermoregulatory dysfunction with narrowing of the thermoneutral zone.
The peripheral vascular system is regarded as the most important correcting variable of thermoregulation. It receives the necessary control signals for vasoconstriction as well as vasodilatation via sympathetic neurones. When core body temperature increases above the set point, peripheral vasodilatation is triggered, resulting in increased blood flow into the peripheral vessels. On the other hand, when temperature falls below the set point, blood flow of peripheral vessels is reduced in order to conserve heat in the body [20].

**Thermoregulatory dysfunction**

Hot flushes represent an excessive reflex response to changes in the temperature control circuit. A variety of disorders in the thermoregulatory centre of the CNS, in the body core or in the peripheral vascular system can induce comparable symptoms. These disorders include generalised diseases, drug-induced effects and changes in the sex hormone milieu. Damage to CNS structures due to injury or disease can also lead to disturbances of temperature homoeostasis. In the case of lesions of the hypothalamus as in patients with multiple sclerosis or after brain trauma, the thresholds for thermoregulatory reactions are significantly altered [39–42]. If there is concurrent hypothalamic damage, posttraumatic hyperthermia may result [43,44].

The classical VMS of a thermoregulatory dysfunction principally affect menopausal women. Hot flushes can, however, also occur in association with malignant diseases, especially with the treatments, such as surgical or pharmacological ovariectomy or antihormone therapy, to affect the levels of circulating estrogen. Hot flushes may occur in breast cancer patients more frequently and more severely than in healthy women [45,46]. Drugs that act on the estrogen receptor (raloxifen or tamoxifen) or on estrogen metabolism (aromatase inhibitors) lead to cellular hypoestrogenemia [47,48]. Hot flushes can also affect men who undergo androgen ablation for treatment of an androgen-sensitive tumour such as prostate carcinoma [49].

**Thermoregulatory dysfunction in the perimenopause**

Even years before the menopause, ovarian function gradually declines and estrogen levels begin to fluctuate [16–18,50,51]. In a review of hormonal changes during the perimenopause, Burger et al. stated that the most remarkable characteristic of the perimenopause was the considerable hormonal variability during this stage of life. Serum levels or periodic secretion patterns of oestradiol are subject to major fluctuations. Women in the perimenopause may present with anovulatory cycles, but then there are also phases in which urinary levels of the estrogen metabolite, estrone, are twice as high as previously determined. Furthermore, even in the perimenopause, estrogen levels can already be constantly low [52,53]. The characteristically unstable estrogen serum concentrations of this phase of life probably have an important role in the origin of VMS, and also of other menopausal symptoms. Together with VMS, the overall complex of these symptoms includes physical (VMA, sleep disturbances, urogenital symptoms), psychological (irritability, depressive symptoms, mood disorders, loss of libido) and somatic symptoms (pain, tiredness) [54–58].

It is not only estrogen concentrations that are subjected to marked fluctuations during the menopause, but also gonadotropin concentrations. The dynamics of secretion of gonadotropins before and around the menopause are characterised by pulsatile release [59,60]. Gonadotropin levels are considerably elevated during and after the menopause; peak serum levels for LH and FSH are found in the early postmenopausal years. During the course of the postmenopause, they gradually fall again to levels approaching those of women in the menstrual cycle [60]. It is important to note a marked temporal relationship between the episodic release of LH and the occurrence of hot flushes. Rises in serum LH secretion almost always coincide with increases in core temperature and hot flushes [61]. However, the rise of gonadotropin LH does not appear to be causally related to the origin of hot flushes, because women with extremely low and apulsatile LH levels, as found under treatment with GnRH analogues, may also develop them. Thus, it appears that the increases in LH secretion are merely temporally associated and not functionally coupled with a heat episode [62].

There are various hypotheses regarding the neuroendocrine cause for vasomotor disturbances in the menopause. The most widely known, originally developed by Tataryn, states that a change in the set thermoregulatory nominal value is not correctly transmitted [38,63]. This results in a narrowing of the thermoneutral zone so that small, usually insignificant increases in core body temperature trigger an excessive thermoregulatory reaction (Figure 3).

Studies by Freedman et al. investigated the connections between core body temperature and the initiation of heat release or heat conservation, and their results provide experimental support for this hypothesis [15,64–67]. Core body temperature was measured using radiotelemetry in symptomatic and asymptomatic menopausal women; the subjects were warmed or cooled and the cooling and sweating thresholds were then measured. The results indicate that the cooling threshold is increased and the sweating threshold reduced [64,67].

In symptomatic menopausal women, a narrowing of the thermoneutral zone from normally 0.4°C to
practically zero may be assumed [15,67]. Hot flushes are generally preceded by a slight increase in core body temperature [65,66]. Heating studies demonstrate that a slight rise in core temperature induces sweating and vasodilatation in symptomatic menopausal women but not in symptom-free menopausal women [15]. These slight changes are tolerated under normal physiological conditions, but in symptomatic women they trigger excessive heat-releasing reactions such as extreme vasodilatation and marked sweating [67].

A further hypothesis regarding the cause of VMS is based on the loss of sensitivity of the peripheral vascular system. The latter represents an important correcting variable of thermoregulation [20]. For temperature homoeostasis to function, changes in skin blood flow as a reaction to thermal changes are essential. Vascular resistance as well as blood flow in the cutis and subcutis are centrally controlled. It is assumed that disturbances in the local reflex thermoregulatory control of skin circulation might contribute to thermoregulatory dysfunction. Changes in vascular sensitivity may reduce the ability of the blood vessels to react quickly and appropriately, thus leading to inadequate thermoregulatory reactions [20]. A delayed reaction of the vascular system to central signals might induce vasomotor disturbances.

Both estrogen as well as progesterone appears to influence the control of skin blood flow [68]. The fluctuations in oestradiol concentrations that occur during the perimenopause can influence the sensitivity of the vascular system by changing the threshold for cutaneous vasodilatation. Low estradiol levels during the postmenopausal period can further contribute to reduced elasticity of the blood vessels and so delay the reaction to changes in body temperature [69].

**Neurotransmitters and hot flushes**

Neurochemical changes probably play a crucial role in the generation of VMS in the menopause [70]. Pharmacological support for this assumption is indirectly provided by the effectiveness of various centrally acting substances in VMS. For example, anticholinergic drugs have been investigated and tested experimentally [71–74]. Other substances such as clonidine (a2-adrenoceptor agonist) and gabapentin have been successfully used in the treatment of VMS [14,19,71]. Another therapeutic approach is regulation of the neurotransmitters serotonin and noradrenaline. Estrogen deficiency in the perimenopause can result in a decrease in serotonin and noradrenaline concentrations [75]. The first studies on selective serotonin reuptake inhibitors (SSRI) and serotonin–noradrenaline reuptake inhibitors (SNRI) suggest high efficacy in the treatment of vasomotor disturbances [76]. SSRI and SNRI were able to reduce hot flushes by up to 65% [77,78]. These substances reduce the reuptake of serotonin and noradrenaline in the presynaptic synapses in the CNS, thereby increasing the supply of these neurotransmitters in the synaptic cleft. This leads to a stabilisation of the thermoneutral zone.
The effectiveness of SSRIs and SNRIs support the hypothesis that neurochemical imbalances in the CNS might be causally involved in the thermoregulatory dysfunction.

**Estrogens as neuromodulators**

Estrogens are potent neuromodulators that intervene in the structure and function of a number of neuronal control circuits in the CNS [79–83]. The human brain reacts to alterations in estrogen levels during various phases of life and adapts to these altered levels. During the fertile years, the CNS develops flexible and sensitive mechanisms in order to adjust and react adequately to the cyclical hormone changes. During the perimenopause, these terminated cycles desynchronise, which can lead to highly variable, even extremely elevated levels of sex hormones (Figure 1) [53]. This necessitates an even higher flexibility of the neuronal reactivity [81,84]. If the CNS cannot adapt itself quickly or efficiently enough, then thermoregulatory dysfunction could result [85].

Estrogens affect the control of gene expression and thereby numerous components of the cellular signal pathway. For example, they are involved in the regulation of membrane receptor proteins, transport proteins and enzymes concerned in the synthesis or degradation of neurotransmitters. In addition, estrogens can also directly affect the membrane fluxes and activation patterns of neurones [80,86,87]. The hypothalamus is particularly affected by such changes because it is highly sensitive to sex steroids due to its stock of functional estrogen and progesterone receptors [79–82]. The hypothalamus is also ascribed a key role in the integration of thermal information and in the control of thermoregulatory reactions [28]. There is a great deal of evidence for the hormonal sensitivity of the hypothalamus, and especially, the POA: estrogens control the functional activity of neurotransmitter systems in this area through specific estrogen receptors [88–90]. Estrogens are also neuromodulators of the serotonergic and noradrenergic systems that probably play a crucial role in the maintenance of thermoregulation in the CNS. Various animal experiments have demonstrated that estrogen receptors are expressed in noradrenergic and serotonergic projections to the hypothalamus [87,91–93] and that estrogen can regulate serotonergic and noradrenergic systems by modulating production, release, reuptake/elimination and receptor activity [50,70].

Effects of fluctuating estrogen levels on neuronal and extracellular concentrations of serotonin and noradrenaline have been studied in relation to thermoregulation in animal models [75,94]. Modulation of these neurotransmitter systems in the POA showed that estrogens affect the synthesis of serotonin and noradrenaline, the density of pre- and postsynaptic binding sites and the deactivation through reuptake and degradation [32,80,95–99]. Estrogens increase the availability of serotonin in the synaptic cleft by increasing the synthesis of the transmitter and slowing its degradation [100–105]. They also regulate the density and binding of serotonin receptors and delay the reuptake of the transmitter from the synaptic cleft [106,107]. The noradrenergic system is also affected by estrogens in terms of synthesis, degradation and receptor function [105,108–110]. Knowledge of noradrenaline plasma levels during the symptomatic phases of hot flushes supports the hypothesis that noradrenaline plays an important role in their origin: before and during the hot flush plasma noradrenaline levels are increased, and the production and release of noradrenaline in the hypothalamus is inhibited by metabolic side-products of estrogen [67,70].

**Adaptation to sex hormone changes**

The first VMS occur in the early perimenopausal transition phase [16]. Because serum sex steroid concentrations fluctuate widely in this stage of life, the VMS occur only temporarily during the perimenopause and can disappear spontaneously [111]. In fact, these symptoms gradually decrease during the postmenopause; however, some women suffer from VMS for long after their last menstruation [16]. The slow progression, reduction and final disappearance of VMS suggest that the brain has to undergo an ‘adjustment’ to a different concentration of hormones and transmitters to regain a thermoregulatory balance. This adjustment period appears to differ between individuals and it can take a considerable time until brain function is newly adjusted, temperature thresholds are reset and normal temperature reactions are restored. There is evidence that the sex hormone largely responsible for VMS is estradiol. In the majority of women whose menopausal VMS are treated with hormone replacement therapy (HRT), the symptoms return after HRT is stopped. Thus, it appears that the VMS are only alleviated, but not completely prevented [8,112]. There could, therefore, be a phase in which brain function is reset and has to be adjusted to the hypoestrogenic state after the menopause. This process called ‘brain adaptation’ supports the hypothesis that changes in neurochemical processes play a role in thermoregulatory dysfunction. Most women adapt to the new hypoestrogenic state although there are individual differences in the extent and duration of the symptoms until adaptation is completed.

**Therapeutic approaches**

There is a range of treatment options for treating vasomotor disorders. The placebo effect has to be
considered in all treatments; a reduction of up to 50% has been reported under placebo [113–115].

**Hormone therapy**

The most effective treatment to date for VMS is hormone therapy [116]; it can almost completely reduce the occurrence of hotFlushes compared to baseline conditions [9]. However, there are short- and long-term risks so that this treatment modality remains controversial. In addition, it is also not available to women for whom hormone therapy is contraindicated.

**Non-hormonal treatment strategies**

Non-hormonal treatments are medically indicated in women with milder symptoms or if contraindications are present. According to the results of the European Menopause Survey 2005, this accounts for 34% of women with menopausal symptoms.

Among the herbal treatment alternatives, the true phytoestrogens that achieve their effects predominantly via the estrogen receptor (e.g. red clover, hops and soya) need to be distinguished from herbal extracts that do not primarily bind to the estrogen receptor but which are nevertheless effective for menopausal symptoms (Cimicifuga). Because the scientific proof for the effectiveness of the herbal alternatives is modest, their value for treating menopausal symptoms cannot be adequately assessed [117,118].

**Antidepressants SSRI, SNRI**

It is especially the SSRI that are playing an increasing role in the non-hormonal treatment of vasomotor symptoms. Prospective randomised, placebo-controlled studies showed a significant reduction in hot flushes of approximately 40–60% as well as an improvement in depression and sleep disturbances under treatment with SSRI (fluoxetine 20 mg/d, paroxetine 12.5–25 mg/d or citalopram 20 mg/d) [119,120] or SNRI (venlafaxine 37.5–75 mg/d) [115]. Positive effects in the treatment of vasomotor disturbances have also been achieved with the substances citalopram and mirtazapine [121]. In contrast to classical HRT, positive effects occur even in the first week of treatment. However, in particular, the substances fluoxetine and paroxetine appear to significantly reduce levels of the active metabolite of tamoxifen (endoxifen), whereas in vitro studies, venlafaxine caused only a very weak modulation of this enzyme effect [122,123].

Desvenlafaxine is a novel SNRI that is being specially developed for the treatment of VMS [124,125]. Initial data on clinical efficacy were published early in 2007 and indicate a good efficacy in vasomotor disorders [75,126]. In a large placebo-controlled study, there was a significant reduction of 65% in frequency and severity of hot flushes over a period of 12 weeks under 100 or 150 mg desvenlafaxine compared to placebo. The long-term effectiveness and also safety was recorded in a large, placebo-controlled study over a period of 52 weeks [127]. In addition, the quality of life was significantly improved through an increase in night-time sleep and a reduction in nocturnal sweating episodes. The most frequent side effects were dizziness, nausea and headache, especially at the start of treatment, but these side effects could be substantially alleviated by dose titration (Figure 4).

![Effectiveness of different treatments for hot flushes](Figure 4. Comparison of the efficiency of possible treatments for vasomotor disturbances (after Loprinzi) [128].)
Anticonvulsant gabapentin

This drug that is used for pain and anticonvulsant treatment leads – as an incidental effect – to a marked reduction in hot flushes. In a placebo-controlled study in breast cancer patients, a dose of 900 mg/day reduced hot flushes by approximately 46%. The main side effects were oedema, dizziness and somnolence [130].

Antihypertensive clonidine

Effectiveness in mild hot flushes has been demonstrated for clonidine [131]. In a comparative study with venlafaxine, the frequency of hot flushes was likewise reduced by 4 weeks of clonidine (2 × 0.075 mg), but efficacy was inferior to that of venlafaxine [129]. It has not proved useful in everyday practice because of its marked side-effects such as sleep disturbances, dizziness and dry mouth (Figure 5).

Conclusions

The number of women who suffer from vasomotor disturbances and whose quality of life is persistently reduced by them is considerable. It is therefore important to offer effective and well-tolerated treatments. As already described, the cause of the thermoregulatory dysfunction appears to be faulty communication in the complex processes between core body temperature, CNS and the peripheral vascular system. In addition ‘brain adaptation’ is a key element in understanding the pathophysiology of thermoregulatory dysfunction.

At the neurotransmitter level, noradrenaline and serotonin play a decisive role because they stabilise the thermoneutral zone. Fluctuating hormone levels modulate these important neurotransmitters and their expression and function. This causes changes in the reaction pattern of thermoregulatory control circuits and in the thresholds for heat and cold responses. Substances which balance these neurotransmitters therefore probably stabilise the thermoneutral zone. The effectiveness of SSRIs and SNRIs in the treatment of VMS has been demonstrated in several clinical trials. It should be emphasised that modulation of a neurotransmitter is not by itself adequate, because there is reciprocal feedback between noradrenergic and serotonergic neurones and every manipulation affects the activity of both neurotransmitters [132].

The most effective treatment to date for VMS is HRT [116], which results in an almost complete reduction in hot flushes [9]. However, hormone therapy is unacceptable under some clinical conditions, for example, after treatment of hormone-sensitive cancers, in pathological blood clotting situations or with hepatic dysfunction. There is thus a great need for a safe and effective hormone-free treatment of VMS, in addition to existing therapeutic options [1]. One alternative is the modulation of neurotransmitter activity by centrally acting drugs. As demonstrated, vasomotor disturbances can be effectively suppressed by pharmacologically balancing neurotransmitters such as serotonin and noradrenaline. SNRI constitute an effective non-hormonal treatment for VMS. This is of great clinical significance, especially for women who cannot take hormones because of pre-existing diseases.
Practical consequences

During the perimenopausal years, hot flushes and night sweats are frequently encountered, indicating derangements in temperature regulation in the hypothalamic temperature-regulating centres. Decreasing estradiol concentrations in the serum and the brain areas of importance for temperature control alter neurotransmitter activity, in particular in the serotonergic and noradrenergic pathways. Therefore, replacing ovarian sex steroids by HRT is the most effective while causal treatment option for VMS. However, contraindications may exist for the use of sex steroids, and therefore steroid-free drugs may be a possible alternative. Our profound understanding of the physiology of thermoregulation, thermoregulatory dysfunction and adaptive processes of the brain may serve as a basis for the development of new therapeutic approaches. On the basis of our current insights in the crucial role of neurotransmitters for the fine-tuning of central nervous temperature control, such agents are consequently characterised as modulators of neurotransmitter activity. Such type of drugs should be free of sex hormone activity and could therefore be used to treat vasomotor disorders during conditions when the use of steroid hormones is contraindicated or undesired. Expansion of the knowledge on the neuroendocrinology of thermoregulation during menopause is therefore essential for exploring new therapeutic ways, in particular the use of steroid-free pharmacological interventions for menopausal vasomotor symptoms.

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