

Hypothesis

The role of serotonin in hot flushes

Hemmie H.G. Berendsen *

Pharmacology Department, N.V. Organon, POB 20, 5340 BH Oss, Netherlands

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Abstract

Hot flushes are experienced in those periods of the female life when estrogen levels are low. Hormone replacement therapy is thus the first choice for treatment of hot flushes. However this treatment is not always accepted or contraindicated for a variety of reasons. Estrogen (and progesterone) strongly interact with a number of neurotransmitters and this has led to a range of non-hormonal treatments including compounds that act via the noradrenergic or dopaminergic systems as well as herbal remedies. These treatments (which are shortly reviewed) are not always successful. Surprisingly, apart from treatment with some selective serotonin (5-HT) reuptake inhibitors (SSRI's), up till now, little attention is given to the strong interaction of estrogens with the serotonergic system. These interactions are shortly reviewed. Based on these interactions, a hypothesis on the genesis of hot flushes is postulated. Especially the 5-HT_{2A} receptor subtype may play a key role in the occurrence of hot flushes. A number of arguments that support this hypothesis are discussed. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Probably the most distressing symptom of the menopausal syndrome is the occurrence of hot flushes. About 80% of all women experience this symptom [1,2] and for some 40% the symptom is troublesome enough to seek for medical help. Hot flushes are not only experienced by menopausal

women, but also occur after bilateral ovariectomy and occasionally in the premenstrual syndrome [3,4].

A hot flush is characterised by a sudden sensation of heat or burning which starts in the head and neck area and then passes, often in waves, over the entire body but particularly marked in the head, neck, upper chest and back. This process is often preceded by a sensation of pressure in the head like a headache. Occasionally palpitations are also experienced. Recently it was found that hot flushes might also be preceded by an increase of core body temperature [5,6].

* Tel.: +31-412-662328; fax: +31-412-662542.

E-mail address: h.berendsen@organon.oss.akzonobel.nl (H.H.G. Berendsen).

The exact pathophysiology of the hot flush is still unknown but it appears to be related to an alteration in the set point temperature in the hypothalamus [7], the area in which thermosensitive neurons or temperature guardian neurons were found [8].

It is generally accepted that estrogens play a main role in the aetiology of hot flushes because they are experienced in those periods when blood levels of estrogens are low or when estrogens are withdrawn as after bilateral oophorectomy. A logical first choice for treatment of hot flushes is thus a hormone replacement treatment with estrogens. Progestogens such as medroxyprogesterone acetate and megestrol acetate, have also been shown to reduce the frequency and intensity of hot flushes [9–11] suggesting that progesterone receptors may be involved in the action of estrogens on hot flushes. This idea is supported by the finding that estrogen induces progestin receptors in the hypothalamus [12], the area in which the central thermoregulating mechanism is located [13].

Despite the fact that hormone replacement therapy is the first option in the treatment for hot flushes, this treatment is not acceptable for a great number of women for a variety of reasons. These reasons may vary from absolute contraindications such as family history for breast or endometrial cancer, impaired liver function etc. to subjective complaints such as fear for undesired resumption of vaginal bleeding or other undesired side effects (for review see [14]) [15]. Therefore a number of non-hormonal compounds are currently used in the treatment of hot flushes.

In this paper first a small review is given of the non-hormonal therapies that are used in the treatment for hot flushes and the role of neurotransmitters in this process. This review is based on data obtained from Medline, but does not claim to be exhaustive. Special attention is given to the interaction of serotonin (5-HT) with estrogens. Consequently a hypothesis is given on a possible mechanism by which a hot flush is generated and how 5-HT might be involved in this process.

2. Involvement of neurotransmitters in the occurrence of hot flushes

Like accelerated bone loss, hot flushes have been counted among the estrogen withdrawal syndrome [16] because they have been shown to occur as the result of a decreased estrogen production during the perimenopausal period or after menopause. However the frequency and severity of the hot flushes show a poor correlation with the blood plasma or serum estrogen level *per se* [17–19]. This suggests that other mechanisms in the central nervous system may play a role. Indeed strong interactions of both estrogens and progestins with several neurotransmitter systems exist within the central nervous system. In an excellent review Casper and Yen [20] described a neuroendocrine basis for the menopausal hot flush and proposed a central role for the opiate-adrenergic interaction. The involvement of catecholamines and endogenous opiates in the occurrence of hot flushes was also suggested by Rebar and Spitzer [21]. More recently Stahl [22] reviewed the strong interactions of estrogens and progestins with the adrenergic, cholinergic, dopaminergic and serotonergic neurons, pathways and receptors.

The close interaction of estrogens with the adrenergic system has led to the use of clonidine and methyl-dopa, both centrally acting adrenergic agonists, as a therapeutic treatment for hot flushes. However, these compounds have reported variable results. In a number of studies methyl-dopa and clonidine have shown to reduce the number and intensity of subjectively experienced hot flushes [23–27], while in others clonidine failed to show a statistically significant reduction of the frequency of hot flushes [28–31]. In one study the reduction in frequency was indeed statistically significant but such small in number that the authors concluded that ‘better means are needed to alleviate hot flushes among patients in whom estrogen therapy is contraindicated’ [32]. In a study in which hot flushes were objectively recorded clonidine was found to reduce the frequency by about 50% after administration of the relatively high dose of 0.4 mg/day, a dose that caused unpleasant side effects in all subjects [33].

The interaction of estrogens with the cholinergic system is mainly related to cognitive functions. It was shown that estrogens enhance the synthesis of acetylcholine, alter the activity of acetyl transferase, alter muscarinic receptors in the hypothalamus and preoptic area and change the electrical firing response to acetylcholine in the hypothalamus ([22] for review). Involvement of estrogens in the occurrence of Alzheimer's disease has also been suggested by several authors (e.g.: [34–36]). Papers dealing with an effect of cholinergic compounds on hot flushes were not found.

The dopamine antagonist veralipride has also been prescribed to counteract the postmenopausal symptoms. A major disadvantage of this treatment is the induction of extrapyramidal disorders such as buccolingual dyskinesias, dyspnea and parkinsonian syndrome [37–39]. Panic like symptoms after withdrawal of this compound were observed [40]. Wide ranges of other compounds are or have been used in the treatment of hot flushes, generally with poor efficacy or with intolerable side effects. These compounds include bromocriptine, a dopamine agonist [41], propranolol and other β -blockers [42] and a series of herbal remedies (see [43] for review). The interaction of estrogens with serotonin is discussed in the next chapter.

3. Interactions of estrogen with serotonin

Presently, 13 distinct human subtypes of serotonin receptor are recognized on the basis of structural, transductional and operational cases, only a gene encoding a putative serotonin receptor has been identified. It would go beyond the scope of this paper to describe the various 5-HT receptors, their localisation, effects and interactions. This has excellently been done by others [44–50], and a nice review of the effects of steroid hormones on the serotonergic system was given by Biegon [51]. It should be noted however that some of the 5-HT receptor subtypes are renamed e.g. 5-HT_{1C} receptors are called now 5-HT_{2C} receptors and 5-HT₂ receptors are named 5-HT_{2A} receptors now [46].

Surprisingly up to date little attention has been paid to the role serotonin (5-HT) could play in the occurrence of hot flushes whereas it is known for a long time that some of the most profound and important actions of estrogens may be exerted at serotonergic systems [52–54]. Blood 5-HT levels have been shown to be dramatically lowered both in spontaneous and surgically menopausal women, thus after estrogen withdrawal, and in both groups the 5-HT level was restored to normal values after treatment with oestriol [55,56]. In menopausal women, treatment with estrogen has been found to augment the serotonergic activity [57] and an increased urinary excretion of 5-hydroxyindol acetic acid (5-HIAA), the main metabolite of 5-HT, was found after estrogen treatment [58]. A low blood estrogen level has been shown to correlate with a high concentration of the 5-HT_{2A} receptor subtype on blood platelets [51] and an upregulation of central 5-HT_{2A} receptors [59]. The 5-HT_{2A} receptor concentration on blood platelets is suggested to reflect 5-HT_{2A} receptor concentration in the brain because it was found in depressive patients that the concentration of 5-HT_{2A} receptors on blood platelets correlate with the severity of depression. And in postmortem studies in brains of depressives that committed suicide 5-HT_{2A} receptor binding was found to be increased [60–62]. The 5-HT_{2A} receptor subtype is also thought to underlie the thermogenesis [63,64]. Stimulation of this receptor may change the set point temperature thereby activating some autonomic functions to cool down the body. An increased skin temperature and sweating are the result. Thus an involvement of 5-HT_{2A} receptors in the aetiology of the hot flushes is strongly suggested.

As already mentioned in the introduction, the effect of estrogens on hot flushes may be an indirect effect via the progesterone receptors since in the hypothalamus estrogen sensitive progesterone receptors have been found [65]. It was shown that serotonin neurons are target cells for ovarian steroids [66,67] and both estrogen and progesterone can alter tryptophan hydroxylase and serotonin transporter gene expression in serotonin neurons [68,69]. Thus also progesterone can have a direct action on 5-HT neuronal function

and thus can influence those affective systems that are under serotonergic control.

4. Possible mechanism by which a hot flush is induced

The involvement of 5-HT_{2A} receptors in the aetiology of hot flushes presumes the following possible mechanism of action for hot flushes. It was repeatedly shown that hot flushes are triggered by a number of external or internal stimuli such as anxiety, ambient temperatures, caffeine, alcohol, spicy food, close physical contact etc. [70]. These stimuli can be considered to be mild stressors and cause an increased cortisol level. In animal studies it has been shown that already mild disturbances cause an increase of corticosterone plasma levels and increase core body temperature [71]. This may resemble the increased core body temperature preceding the hot flush as observed by some authors in menopausal women [5,6]. In- or external stimuli also cause an immediate release of 5-HT via 5-HT moduline, an endogenous tetrapeptide (Leu-Ser-Ala-Leu) which has recently been isolated from mammalian brain [72]. This peptide was shown to specifically interact with 5-HT_{1B} autoreceptors as a non-competitive antagonist [73]. It was demonstrated that activation of the 5-HT_{1B} receptor-related transduction system could be blocked by 5-HT moduline and that the inhibitory effect of a 5-HT_{1B} receptor agonist on the neuronal release of 5-HT was markedly decreased [74]. 5-HT moduline has also been shown to act as an important modulator of the 5-HT-mediated adaptation to stress [75]. After mild stress (i.e. anxiety, high ambient temperature, coffee alcohol etc.) a strong increase of 5-HT moduline in the cortex, hippocampus and hypothalamus has been seen leading to an extra release of 5-HT in these areas. Since the 5-HT_{2A} receptors in the hypothalamus are upregulated after estrogen withdrawal [51] these receptors are activated by the 5-HT release. This results in a disturbance of the thermoregulatory system in the hypothalamus. In reaction some autonomic functions are activated to cool down the body (increased skin temperature and sweating). The

autonomic functions may include vasodilation especially of the peripheral arteries from which it was shown in animal experiments that their diameter was reduced after ovariectomy [76]. An influence of direct activation of vascular 5-HT_{2A} receptors on this vasodilation may also play a role [49]. In Fig. 1 this process is schematically given.

Besides hot flushes menopausal women also often experience nocturnal sweating. The mechanism that causes this sweating is most likely the same as the mechanism that induces hot flushes. During sleep dreams occur. These dreams can be considered to be the stress factor to trigger a release of 5-HT that, via activation of the 5-HT_{2A} receptors, results in sweating and/or a hot flush. Support for this idea is found by Scharf and colleagues [77] who found that estrogen therapy, and a consequent downregulation of 5-HT_{2A} receptors, resulted in an improvement of sleep efficiency and a reduction of cyclic alternating patterns of sleep (CAPS). These CAPS are associated with nocturnal arousals. The overall number of hot flushes and the number of hot flushes associated with nocturnal awakenings were also reduced by the estrogen treatment. This suggests that after estrogen the frequency of nocturnal arousal's decreases and sleep quality improves in conjunction with reduction in the rate of CAPS.

Seen the above outlined possible mechanism on the genesis of a hot flush one can postulate the following hypothesis (see also Fig. 1): A strong reduced estrogen level leads to a strong reduction of the blood serotonin level and consequently to an upregulation of 5-HT_{2A} receptors. If women are then (mildly) stressed by some in- or external stimulus these 5-HT_{2A} receptors are stimulated by the extra released 5-HT, because the feedback mechanism via the 5-HT_{1B} autoreceptor is blocked by the stress induced release of 5-HT moduline. The hypothalamic set point temperature is disturbed by the activation of 5-HT_{2A} receptors and autonomic reactions to cool down the body such as vasodilation causing increased skin temperature [78] and sweating are activated. A hot flush is the result.

5. Clinical and preclinical observations that support this 5-HT hypothesis for hot flushes

The hypothesis for the involvement of 5-HT in the genesis of a hot flush is supported by several findings in which 5-HT plays a role:

1. Effect of blockade of 5-HT_{2A} receptors. Treatment of menopausal women with the 5-HT₂ and 5-HT₃ receptor blocker mirtazapine [79,80], was found to reduce the frequency and intensity of hot flushes. This effect had a short onset of action [81,95] and after stopping the

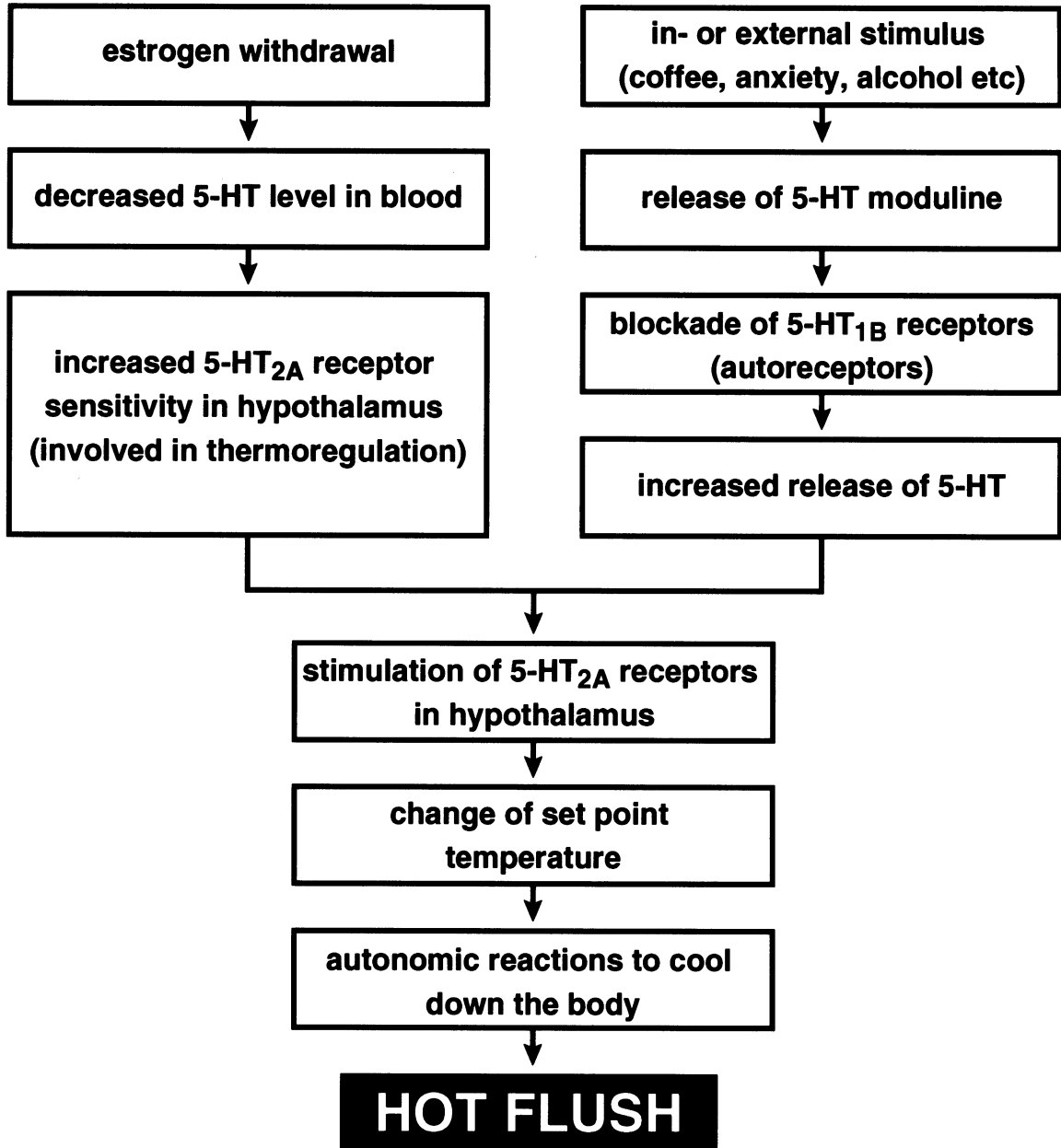


Fig. 1. Possible mechanism by which a hot flush is induced.

treatment with mirtazapine an almost immediate recurrence of hot flushes was seen [95]. Treatment of menopausal women with the 5-HT₂ receptor blocker mianserin was also shown to be effective in treating hot flushes [82]. Thus a direct blockade of 5-HT₂ receptors seems to have a beneficial effect on hot flushes.

2. Effect of activation of 5-HT_{2A} receptors. It has been reported that activation of 5-HT₂ receptors with m-Chlorophenylpiperazine (m-CPP), a 5-HT_{2A/2C} receptor agonist [83], induces ‘sweating and hot and cold flashes’ [84], ‘flushes’ [85], ‘palpitations and sweating’ [86] and ‘hot flushes and cold chills’ [87]. In these studies a relatively high dose of m-CPP was used. If 5-HT_{2A} and 5-HT_{2C} receptors have to compete for their effect, as in the case with m-CPP, the 5-HT_{2A} receptor mediated response takes precedence [88]. A disturbed thermoregulatory system leading to a hot flush is the result.
3. Effect of selective 5-HT reuptake inhibitors (SSRI’s). In a retrospective chart review of 15 patients, Trott and colleagues [89] found hot flushes subjectively ameliorated after treatment with the SSRI sertraline. Sertraline was also found to reduce the frequency and severity of hot flushes secondary to medical castration as treatment of advanced prostate cancer [90]. The mixed 5-HT- and noradrenaline reuptake inhibitor venlafaxine has also been shown to reduce the frequency and severity of hot flushes in women with a history of breast cancer [91]. Venlafaxine was also effective in men treated for hot flushes after androgen ablation therapy for prostate cancer [92]. Of course these are just preliminary studies that need to be confirmed in a sound double blind, placebo controlled clinical study. Nevertheless they suggest that inhibition of serotonin reuptake might be effective in the treatment of hot flushes. This effect of the reuptake inhibitors may seem to contradict the idea of blockade of the 5-HT receptors. However, in animal studies it was shown that the stimulus properties of 5-HT reuptake inhibitors completely resemble

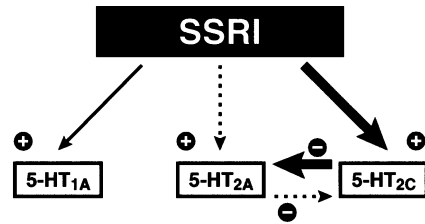


Fig. 2. Effect of a selective serotonin reuptake inhibitor (SSRI) on some 5-HT receptor subtypes. For explanation see text.

those of 5-HT_{2C} receptor agonists, to a small extent those of a 5-HT_{1A} receptor agonist, but not those of a 5-HT_{2A} receptor agonist [93]. It was also shown that 5-HT_{2A} and 5-HT_{2C} receptors functionally interact. Activation of one receptor causes inhibition of the effect induced by the other receptor [88]. Thus activation of 5-HT_{2C} receptors causes similar effects to blockade of 5-HT_{2A} receptors (see Fig. 2). This means that if hot flushes are induced by activation of 5-HT_{2A} receptors, they might be inhibited by concomitant activation of 5-HT_{2C} receptors and, because they possess similar stimulus properties as 5-HT_{2C} receptor agonists, by SSRI's.

4. Estrogen and progestogen treatment have been shown to have a beneficial effect on hot flushes. However, the effect of these steroids is only seen after a longer treatment time (mostly 2 weeks). This delay in efficacy may be explained by the mechanism by which these compounds act. It was seen that after treatment with estrogens the decreased blood serotonin level in menopausal women was restored [55,56]. Thus the sensitised 5-HT_{2A} receptors as a result of the low estrogen level, have to be downregulated first after hormone treatment and this takes some time. The same mechanism but now in the opposite direction may be responsible for the delay in recurrence of hot flushes after stopping the treatment with estrogens or progestogens [10,94]. This idea is supported by the fact that during the first days after treatment with progestagens an increased number of hot flushes are seen [10]. In this period the 5-HT_{2A} receptors are still supersen-

sitive whereas the blood level of 5-HT increases by the progestagen treatment. The sensitised 5-HT_{2A} receptors are then activated strongest by the increased 5-HT level. Anecdotal clinical reports state that hot flushes are seen within 24 h of ovariectomy indicating that estrogen withdrawal may also cause a rapid induction of hot flushes suggesting that the delay in effect after treatment with estrogens could be due to pharmacokinetic mechanisms. However if this was the case than the increase of hot flushes after treatment with progestogens as seen by Loprinzi and colleagues [10] should not occur. Thus pharmacokinetic mechanisms underlying the delay of estrogen effects can not completely be excluded but may not be likely.

5. In an animal model it was found that the fall in tail skin temperature during the transition from the light to the dark period was attenuated after estrogen withdrawal through ovariectomy. This effect is seen on the third day after ovariectomy. Treatment with estrogen or the 5-HT₂ receptor antagonist mirtazapine restored this attenuated fall in tail skin temperature. The effect of estrogen was seen on the third day of treatment whereas the effect of mirtazapine was already seen on the first day of treatment (Berendsen et al., in preparation). This suggests again that the effect of estrogen may be indirect e.g. via down regulation of the 5-HT_{2A} receptor, whereas blockade of the 5-HT_{2A} receptors causes an immediate effect.

Hot flushes are experienced for several years during the perimenopause and after the menopause. Then they disappear. None of the above given arguments can explain why these hot flushes after some time, gradually disappear spontaneously. It might be speculated that the disturbed balance between the different 5-HT receptor subtypes (i.e. the upregulated 5-HT_{2A} receptor) is spontaneously restored after some time. It might also be possible that an adaptational mechanism is triggered whereby hot flushes are reduced and disappear in the end.

6. Conclusions

The strong interaction of estrogens and progestins with the serotonergic system and the different preliminary clinical findings with serotonergic compounds have led to the hypothesis that serotonin is strongly involved in the pathogenesis of hot flushes. The 5-HT_{2A} receptor seems to play a prominent role in this respect. If this hypothesis is true, it opens the possibility to treat hot flushes with compounds with a very short onset of action. This hypothesis could be tested in double blind and placebo controlled clinical studies with mirtazapine, mianserin or compounds with similar activity. In these experiments plasma levels of 5-HT and 5-HT_{2A} receptor density on blood platelets, as an index of central 5-HT_{2A} receptor density, should also be measured. If hot flushes are subjectively scored, placebo groups have to be included in these experiments because it is known that placebo treatment may reduce the frequency of hot flushes by up to 20% [10,94]. A good alternative would be the objective measurement of hot flushes as was done before [33].

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