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Prostate Carcinoma and Hot Flashes

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1. Introduction

In prostate cancer patients, the use of hormonal-deprivation (HD) therapies, such as the gonadotrophin-releasing hormone analogues (GnRHa) or luteinizing hormone releasing hormone analogues (LHRHa), antiandrogens, or bilateral orchiectomy, induces a range of hormone-related symptoms. Hot flashes (HF) are one of most common and distressing symptoms that can occur. Other signs and symptoms caused by estrogen and androgen deprivation are metabolic syndrome, increased cardiovascular risk, loss of libido, erectile dysfunction, accelerated osteopenia/osteoporosis, increased bone fractures, neurocognitive dysfunction, weight gain, decreased muscle mass, etc.

Since the pioneering studies by Huggins and Hodges (Huggins & Hodges, 1941), hormonal manipulation in which tumor cells are deprived of hormonal steroids has gained increasing relevance in the treatment of some types of cancer. They reported episodes of HF in 9 of 21 castrated patients 2 to 3 weeks after surgery (Huggins & Hodges, 1941).

Surgical castration, the most commonly used procedure to obtain HD a few years ago, has been gradually replaced by medical castration with the addition of LHRHa. After orchiectomy, approximately 50% of the patients experienced HF within months (Charig & Rundle, 1989; Maatman et al., 1985; Aksel et al., 1976; Buchholz & Matarelli, 1994).

The incidence of HF is 60-75% with the use of LHRHa (Harvey et al., 1985; Leuprolide Study Group, 1984; Sarosdy et al., 1999; Parmar et al., 1987). The reason why this incidence rate is higher than that observed with surgical removal is not well understood. As is the case with orchiectomy, HF occur over several months and may persist, although with less intensity, for many years.

Hot flashes are a major clinical problem in many cancer patients undergoing HD (Charig & Rundle, 1989; Nishiyama et al., 2004; J. S. Carpenter et al., 2004), as demonstrated by the quality of life studies.

While HF are not considered a serious adverse effect, their frequency and severity may be bothersome and can impair patients' quality of life. Thus we need to understand the mechanism of hot flashes and use this information to develop patient-tailored therapies to address these symptoms.

The purpose of this chapter is to discuss theories, to observe how they are reflected in the pathophysiology of HF, and to describe current treatments.

2. Pathophysiology

Hot flashes are characterized by a subjective sensation of heat perceived mainly in the upper part of the chest, followed by excessive perspiration. The major symptom is the subjective

feeling of heat which may last several (4 to 10) minutes, and may be associated with other clinical complaints such as anxiety, irritability, palpitations, blushing, panic, and a sensation of loss of control, along with significant physical and emotional distress (Albertazzi, 2006). A mean rise of 0.9º C in body temperature is detected between 7 and 20 minutes before the hot flashes, with an ensuing increase in both the energy expenditure and the respiratory quotient (J. S. Carpenter et al., 2004).

Generalized peripheral vasodilatation typically appears within the first seconds of the episode (Molnar, 1975; F. L. Kronenberg et al., 1984). In addition, an increase in sweating and electric conductance are observed, with a strong correlation between both parameters (Molnar, 1975). During a HF a 30-second rise of 2-μS in skin conductance occurs (Robert R Freedman, 2005; J. S. Carpenter et al., 1999). Independently of the patient's perception, the measurement of skin conductance might be used for the clinical monitoring of HF, since it can be recorded on an outpatient basis by means of a Holter-like system. In such cases, a close correlation exists between these recordings and those obtained from daily data-collection questionnaires (Robert R Freedman, 2005; J. S. Carpenter et al., 1999).

There are many hypotheses about the mechanism of HF (**Figure 1**). We will proceed to explain the most important ones.

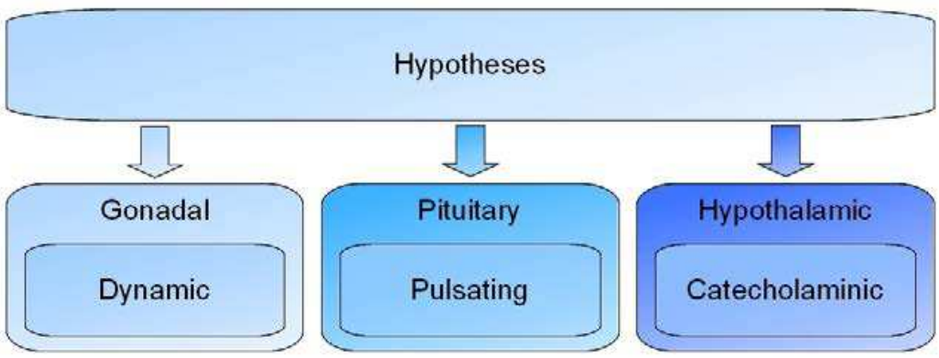

Fig. 1. Different hypotheses on the mechanism of hot flashes

2.1 Gonadal hypothesis

Since HF are commonly associated with orchiectomy in men and with menopause and ovarian failure in women, it may be assumed that they are causally related to low sex hormone levels.

It is necessary to remember that estrogens come from androgens. Aromatase cytochrome P450 is the enzyme that is responsible for estradiol biosynthesis from testosterone.

The hormone deprivation theory applied to prostate and breast carcinoma patients seems appealing and is based on the occurrence of HF following both medical and surgical castration. The responses to hormone replacement therapy and the effects following its withdrawal further support this hypothesis. However, an argument against this hypothesis is the absence of HF in patients with congenital hypogonadism (Turner and Kallman syndromes) as well as in prepubertal children (Kouriefs et al., 2002). These scenarios suggest that HF result from the dynamic reduction or sudden deprivation of sex hormones rather than their absolute plasma concentration. The **Dynamic hypothesis** is currently the most widely accepted theory (Kouriefs et al., 2002).

2.2 Pituitary hypothesis

In 1976, Alksel (Aksel et al., 1976) argued against the deprivation hypotheses. After suggesting that HF occurred due to a rise in gonadotrophin levels, he postulated a pituitary rather than a gonadal cause for this phenomenon. His theory is supported by studies performed on premenopausal women in whom a correlation was found between HF and the levels of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Melldrum et al., 1984). Casper (Casper et al., 1979) and Tataryn (Tataryn et al., 1979) demonstrated a synchrony between LH peaks and HF, which led them to propose a **pulsating hypothesis**. However, it must be noted that LH surges are not consistently associated with HF, although all hot flash episodes do coincide with an LH peak.

2.3 Hypothalamic hypothesis

In postmenopausal women, no correlation has been seen between gonatropin levels and HF (Linsell & Lightman, 1983). Also to be noted is the absence of HF in patients with Klinefelter syndrome in whom constitutively high gonadotrophin levels are found, and in other treated patients with high induced gonadotrophin levels (such as those used in ovulation-inducing protocols). HF does appear, however, after a hypophysectomy and during the LHRHa therapy for prostate cancer.

As a result of these findings, many investigators have suggested a potential role for the hypothalamus in the pathophysiology of HF (Kouriefs et al., 2002).

The similarities between HF and adrenergic symptoms have led to theories regarding the potential involvement of catecholamines (Albertazzi, 2006) in the hypothalamic hypothesis. After failing to show a correlation between HF and peripheral catecholamine levels, Casper (Casper et al., 1979) postulated the involvement of central pathways. On the other hand, some evidence points to noradrenaline (NA) as the hypothalamic neurotransmitter responsible for HF. Animal experiments have shown that the intrahypothalamic administration of NA affected thermoregulation (Albertazzi, 2006). Furthermore, high peripheral concentrations of MHPG (3-methoxy-4-hydroxiphenylglycol) — the major brain NA metabolite— during HF were found, while no changes in VMA (vanilmandelic acid) —a peripherally produced NA metabolite— were seen (R R Freedman, 2001).

Additional evidence to support this **catecholaminic hypothesis** (**Figure 1**) is the finding that the administration of yohimbine (an α_2-adrenergic antagonist) to symptomatic women increases hypothalamic NA concentrations and induces HF that subside after administration of clonidine (an α_2-agonist) (R R Freedman et al., 1990). The increased sympathetic activation, mediated by the α_2-adrenergic receptor, plays a major role in the occurrence of HF. Since α_2 receptors are modulated by estrogens, abrupt estrogen deprivation is likely to contribute to the development of HF via this pathway (Etgen et al., 2001). Exposure to high temperatures and hot drinks generates a reduction in the number of α_2 receptors, which is followed by a further release of additional amounts of NA and the appearance of HF (Kouriefs et al., 2002).

On the other hand, the hypothalamic thermoregulatory center is anatomically very close to the LHRH producing center (de Boer et al., 2009). (**Figure 2**)

Increases in hypothalamic NA caused by HD are thus likely to both stimulate LHRH producing neurons and activate the heat-losing mechanisms controlled by the adjacent thermoregulatory center (R R Freedman & Krell, 1999; Dacks & Rance, 2010). It has also been

observed that high NA levels trigger HF by lowering the sweat-flash threshold in symptomatic postmenopausal women (Albertazzi, 2006).
The relation between sex steroids and hypothalamic cathecolamines remains unclear. The catecholestrogen (2-hydroxiestrogen) theory is based on the fact that the chemical structure of catecholestrogens, the most common estrogen metabolites, is similar to that of catecholamines (Paul & Axelrod, 1977).

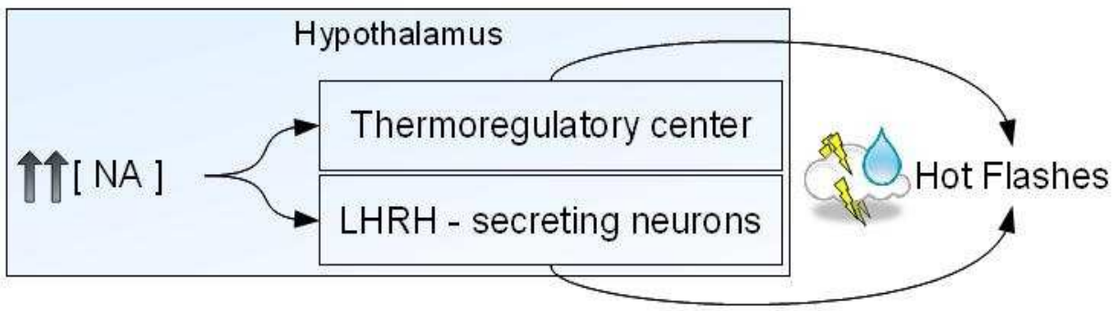

Fig. 2. Direct effect of noradrenaline on hypothalamic nucleus to trigger hot flash mechanism

Hypothalamic catecholestrogen concentrations are ten times greater than those of estrogens. Catecholestrogens act on the enzymes catecholmethyltranspherase and tyrosinhydroxilase which, in turn, influence the synthesis and breakdown of catecholamines, thus reducing NA levels. Therefore, low hypothalamic catecholestrogen concentrations will result in an increase of NA levels and the onset of HF. (**Figure 3**)
Opioids are also implicated in the pathogenesis of HF. Stubbs et al. (Stubbs et al., 1978) induced HF with the administration of opioids to healthy volunteers. Naloxone, an opioid antagonist, causes vasomotor symptoms when administered to opioid-dependent animals (Tulandi et al., 1985). Sex steroids induce the hypothalamic production of β-endorphins, which are endogenous hypothalamic opioids that inhibit catecholamine synthesis by reducing the activity of the estrogen-2-hydroxilase (Fishman et al., 1980). Peripheral sex hormones promote the formation of catecholestrogens as well, which in turn block the hypothalamic synthesis of NA (Robert R Freedman, 2005). (**Figure 3**) Therefore, a sudden deprivation of sex hormones will result in decreased endorphin levels and loss of negative feedback (R R Freedman & Krell, 1999).
The ensuing rise in hypothalamic NA levels eventually enhances the release of LHRH by the LHRH-secreting neurons. NA also acts on the thermoregulatory center by shortening its response range, lowering its temperature tolerance thresholds, and generating HF, which in turn enhances heat loss (Robert R Freedman, 2005; R R Freedman & Krell, 1999). (**Figure 2**)
At the regulatory center, there is a zone for the control of body temperature. At the lower threshold, a shivering mechanism is triggered, leading to a rise in temperature. At the upper threshold, heat loss is induced through skin vasodilatation and profuse sweating. Between these two thresholds is a thermoneutral zone (Savage & Brengelman, 1996). (**Figure 4**)

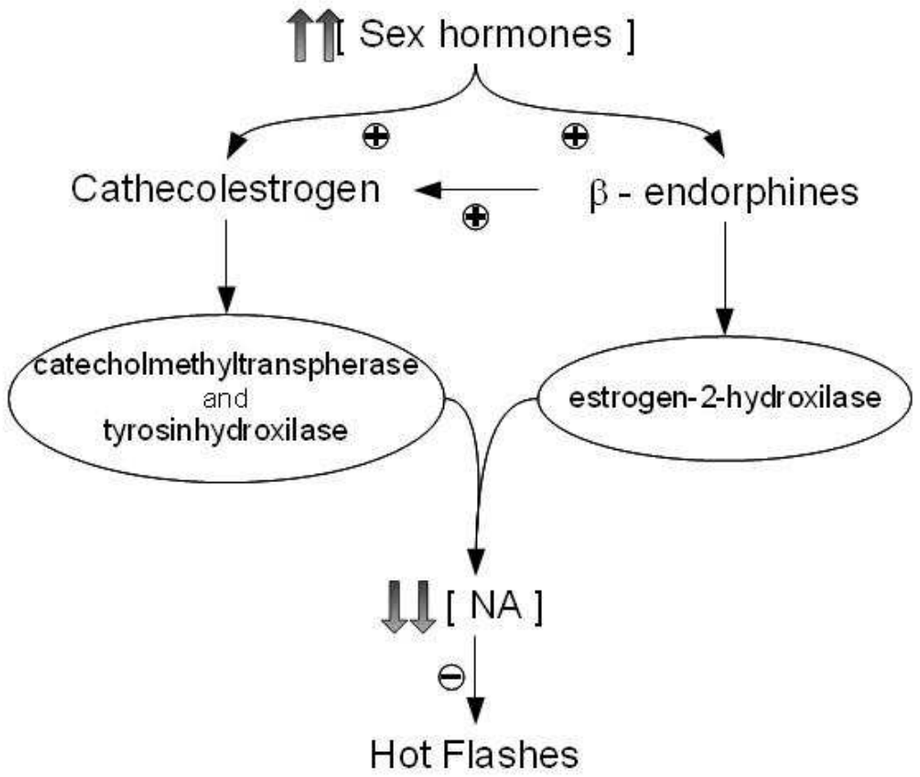

Fig. 3. Negative impact of sex hormones on noradrenaline production

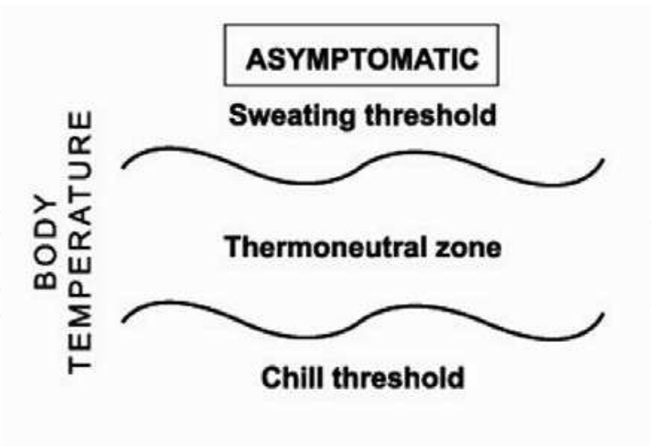

Fig. 4. Body temperature control range in an asymptomatic patient

In patients with HF, the thermoneutral zone is quite narrow, which is why small changes may influence the thermoregulatory center (Robert R Freedman, 2005; Dacks & Rance, 2010). (**Figure 5**) The increase in body temperature after a rise in ambient temperature or the intake of excessively hot food exceeds the upper threshold of the thermoneutral zone and triggers the heat-dissipating mechanisms (Dacks & Rance, 2010; Savage & Brengelman, 1996).

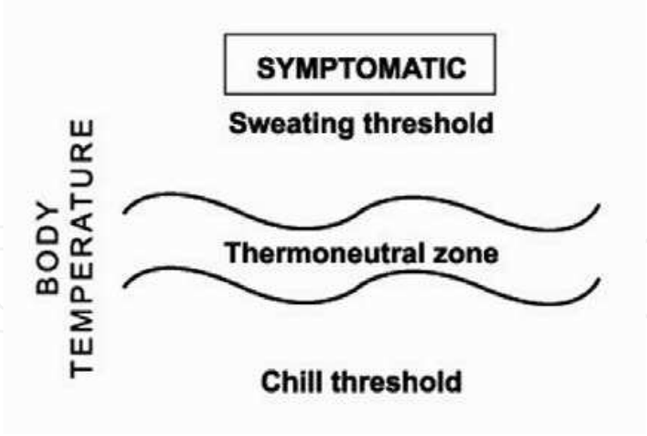

Fig. 5. Body temperature control range in symptomatic patient

The increase in hypothalamic levels of certain substances, such as noradrenaline, tends to narrow this zone, while other agents such as serotonin and dopamine have the opposite effect (Berendsen, 2000). (**Figure 6**) It has been concluded that the thermoneutral zone is 0.4 ºC in asymptomatic and 0.0 ºC in symptomatic patients (Robert R Freedman, 2005).
Serotonin (5-hydroxytryptamine or 5-HT) levels are reduced in postmenopausal women, even though they normalize following replacement therapies.
A sudden deprivation of sex hormones results in a reduction of circulating serotonin, with a parallel increase in its 5-HT2A hypothalamic receptors. These receptors may also play a role in the pathogenesis of HF (Albertazzi, 2006).

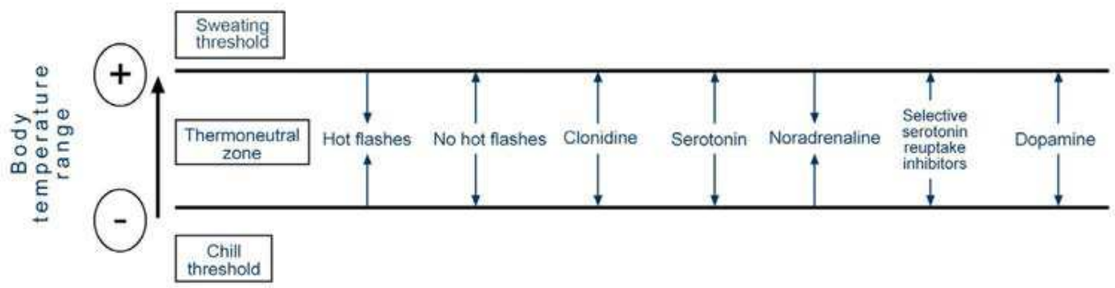

Fig. 6. Effect on thermoneutral zone of various substances

To sum up, a basic feature in the pathogenesis of HF is the negative effect of plasma sex hormones on the hypothalamic secretion of noradrenaline, as well as its balance with serotonin and dopamine. (**Figure 7**)
Other information supports the hypothalamic hypothesis. It has recently been demonstrated that serum IL-8 concentrations were significantly higher in women with HF than without HF. IL-8 could play an important role in the pathophysiology of HF (Yasui et al., 2006; Noguchi et al., 2008).

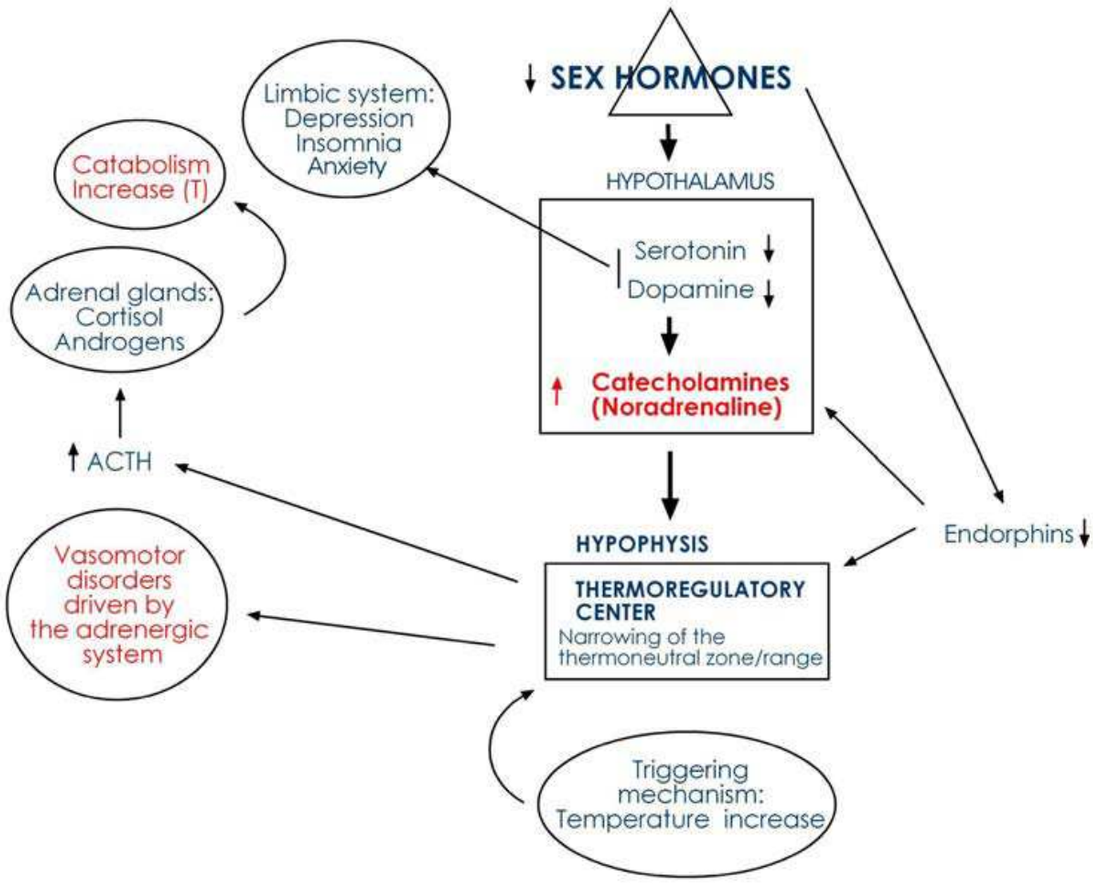

Fig. 7. Negative effect of sex hormones on hypothalamic noradrenaline

The rat ortholog of the human IL-8 receptor has been identified (Dunstan et al., 1996), and the functions of IL-8 appear to be performed by cytokine-induced neutrophil chemoattractant (CINC) in rodents (Guex-Crosier et al., 1996). It has been shown that CINC stimulates the secretion of prolactin, GH, and ACTH but suppresses the secretion of LH and FSH from the anterior pituitary cells (Koike et al., 1994). In animal models HF could be triggered by intracerebroventricular injection (i.c.v.) of LHRH analogues (Noguchi et al., 2008; Noguchi et al., 2003). After that, an increase of CINC around the periventricular area in the hypothalamus is observed in ovariectomized rats.

Hypothalamic thermoregulation by CINC and LHRH may, therefore, be a reciprocal relationship. However, changes in CINC concentration and skin temperature after i.c.v. injection of LHRHa were reversed by replacement of estradiol. Therefore, there may be a feedback regulation mechanism involving LHRH and CINC through the hypothalamus-pituitary-gonadal axis (Noguchi et al., 2008).

Consequently, LHRH and CINC play a key role in the homeostasis of body temperature in HD situations (Noguchi et al., 2008). All these finding support the **hypothalamic hypothesis**.

New aspects of hot flash research, including neuroimaging and the study of genetic polymorphisms, when combined with increasingly nuanced ways of asking questions of

culturally distinct populations, pose challenges, but at the same time offer a rich complexity from which a better understanding of hot flashes will emerge (F. Kronenberg, 2010).
Other parts of the brain can be seen to be involved in the development of hot flashes. Magnetic resonance imaging has shown activation of the insula and anterior cingulated cortex during hot flash episodes (F. Kronenberg, 2010).
Finally, genetic variation in CYP19 and sex hormone binding globulin contributes to variance in circulating hormone levels between postmenopausal women, and it could potentially have an influence on hot flashes (Dunning et al., 2004).

3. Current treatment of hot flashes

As is to be expected, the great majority of published studies were carried out in menopausal women or in breast cancer survivors, but more and more trials are being conducted in patients undergoing hormone deprivation for prostate cancer.
In view of their pathophysiology, the regulatory mechanisms on negative feedback should be taken into account as causes of these hot flashes.

3.1 Hormone replacement

Hormone replacement with estrogens was the first treatment used in the 20th century. Other forms of replacement included progesterones and androgens, but because of the hormone sensitivity of prostate cancer, the latter would be contraindicated.
As for estrogens, it should be noted that despite their high efficacy even at low doses, they have negative side effects. These include thromboembolic phenomena, cardiovascular morbidity and painful gynecomastia (J. A. Smith, 1994; J. I. Miller & Ahmann, 1992; Atala et al., 1992).
The most widely used estrogen, both orally and transdermally, is estradiol (Shanafelt et al., 2002), which requires at least a month to obtain benefits. Higher doses provide better control of symptoms than lower doses but also have more side effects, though these are fewer when transdermal formulations are used. The usual oral doses are ≥ 0.25 mg/day, whereas the daily amount required for patches is less than 0.05 mg/day.
In summary, estrogen therapy shows a dose-dependent response, with a balance in favor of transdermal therapy and an efficacy of 80-90%, reducing the number of hot flashes by 2.5 to 3 hot flashes daily (Rossouw et al., 2002; Nelson, 2004), but with undesirable side effects that need to be considered (Kouriefs et al., 2002; Rossouw et al., 2002). Its effectiveness was confirmed in a 2002 meta-analysis from the Cochrane Library, in an extensive review published in JAMA in 2004 (Nelson, 2004), and in a more recent systematic review in Lancet Oncology (Frisk, 2010).
Progesterones, like estrogens, stimulate the production of hypothalamic β-endorphins. Their use is also not free from undesirable side effects (C L Loprinzi et al., 1994; Quella et al., 1998; C L Loprinzi et al., 1992). There is experience in both men and women, and the most used is megestrol acetate, with starting doses of 20 mg twice daily and subsequent reduction to the lowest effective dose, with response rates of 80-90% (Frisk, 2010; J. W. Goodwin et al., 2008; Quella et al., 1998; C L Loprinzi et al., 1994).
As a second drug in use, cyproterone acetate is a steroidal antiandrogen with progestogenic action. It shows response rates comparable to megestrol acetate but with risk of hepatoxicity, fatigue, painful gynecomastia and galactorrhea (Frisk, 2010). Treatment for hot flashes should be started at 50 mg/day, and not exceed 300 mg/day (Moon, 1985; Irani et al., 2010).

Lastly, we need to mention medroxyprogesterone acetate given in 20-40 mg oral doses daily with equal or superior efficacy to megestrol or a single 400 mg i.m. depot dose with an effect sustained over at least 6 months (Irani et al., 2010; Prior et al., 1995). Although some experts consider 400 mg to be a very high dose, it is a small dose if we compare it to the 500 mg intramuscular or oral doses used daily during months for the treatment of breast cancer. It was found to be correctly tolerated and weight gain was the only undesirable effect.

There have been reservations regarding the use of progesterones in prostate cancer because it has been reported in some articles to be related to increases in PSA levels (Dawson & McLeod, 1995; Wehbe et al., 1997). Clarification is still required before these results can be extrapolated to support the use of low-dose progesterones in the treatment of prostate cancer, although their antitumor activity has also been reported in breast, endometrium and prostate cancer (Wentz, 1985; Bonomi et al., 1985).

The effect of estrogens and progesterones can persist for extended periods after their withdrawal (C L Loprinzi et al., 1994; Haas et al., 1988).

The problems of the use of hormone replacement therapy in menopausal women have acquired a certain prominence as a result of the publication of the results of the Women´s Health Initiative randomized controlled trial, which reveal the increased risk of developing breast cancer, cognitive disorders, cardiovascular and thromboembolic disease. Alternative treatments are therefore desirable.

The absolute risks per 10,000 person-years were 7 more coronary events, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. They also reduced vasomotor symptoms and vulvovaginal atrophy (G. L. Anderson et al., 2004).

3.2 Non-hormonal therapies

The current availability of non-hormonal therapies is a major advance both for women who have survived breast cancer and for men with a prostate adenocarcinoma undergoing hormone deprivation, in whom hormone replacement therapy may be contraindicated due to adverse effects.

Several drugs have been tested for the management of vasomotor symptoms. A 2006 meta-analysis of well-designed studies (Nelson et al., 2006) showed that the only effective therapies are, in increasing order of effectiveness: gabapentin, selective serotonin-reuptake inhibitors, and clonidine. A brief description of these therapies is discussed below. Their efficacy is slightly less than with hormone replacement, but their effectiveness has been widely demonstrated.

Since noradrenaline is the neurotransmitter involved in the control of the thermoregulatory center, the blockade of both α- and β-adrenoceptors may provide symptomatic relief. On this basis, the α_2 agonist clonidine (Clayden et al., 1974) has been tested in both men and women (Pandya et al., 2000). Alpha$_2$ receptors have been identified at both hypothalamic and peripheral levels. Their presynaptic activation brings about a decrease of NA release (R R Freedman & Dinsay, 2000). They are also peripherally active by reducing vasodilatation, which contributes to improved control of hot flashes (Kouriefs et al., 2002). Although higher doses are associated with a more significant symptomatic relief, they also involve a greater toxicity. Transdermal administration (Nagamani et al., 1987) results in equivalent absorption to oral administration, but is associated with more common skin reactions. Recommended

doses are between 25 to 400 µg. Its efficacy is lower than that of hormonal therapy (20-55%), and side effects are common. Two recent double-blind randomized-controlled clinical trials and a systematic review, comparing clonidine to venlafaxine, have reported conflicting results (Frisk, 2010; Buijs et al., 2009; Loibl et al., 2007). The drug may be potentially useful when other therapies are contraindicated (Kouriefs et al., 2002).

Response rates of 44-60% have been achieved with gabapentin 300 mg every 8 hours, with the main side effects being somnolence, dizziness, fatigue, skin rash, palpitations, and peripheral edema (Charles L Loprinzi et al., 2007; C L Loprinzi et al., 2009). In a recent open-label, randomized, cross-over trial gabapentin is worse tolerated than Venlafaxine (Bordeleau et al., 2010).

Its mechanism of action, although at present unclear, may involve the modulation of calcium channels (T. J. Guttuso, 2000). In a recent study, gabapentin has been shown to be useful in patients with an inadequate response to antidepressants (Charles L Loprinzi et al., 2007).

Some serotonin-acting antidepressants may be of value in the management of hot flashes. As mentioned above, serotonin levels, which are decreased in postmenopausal women, tend to normalize after replacement therapies. Thus, an abrupt fall in sex hormones is likely to produce a decrease in circulating serotonin along with an up-regulation of their 5-HT_{2A} hypothalamic receptors (Albertazzi, 2006; Curcio et al., 2005), which may be involved in the pathogenesis of hot flashes.

The potency of 5-HT_{2A} antagonists varies widely among the first generation (tricyclic) antidepressants, although the resulting impact on the therapeutic activity of these drugs has not yet been defined. Another class of antidepressants, known as phenylpiperazines, has been shown to be more selective than tricyclics and to possess more potent $5HT_{2A}$ receptor-blocking activity.

Newer antidepressants, mainly venlafaxine, desvenlafaxine and paroxetine, play an important role in the non-hormonal therapy of hot flashes (Albertazzi, 2006). Observed response rates are approximately 50-69 %, somewhat lower than those achieved with hormonal therapies; however, their improved safety profile in cancer survivors makes them an appealing option for this group of patients. Serious side effects are rare, since the doses used are lower than those normally given for the treatment of depression, and a withdrawal syndrome has not been associated with such doses (Irani et al., 2010; Buijs et al., 2009; Loibl et al., 2007; C L Loprinzi et al., 2000; Archer et al., 2009).

There is little data regarding the use of new-generation antidepressants for the treatment of hot flashes in prostate cancer patients undergoing hormone deprivation. Venlafaxine has been shown to produce symptomatic relief in a study involving 16 patients (Quella et al., 1999). Another small study with 24 patients reported symptomatic relief of hot flashes in men who received paroxetine for 5 weeks (Charles L Loprinzi et al., 2004). **(Table 1)**

However, the use of selective reuptake inhibitors such as paroxetine during tamoxifen treatment must be evaluated with caution, as it is associated with an increased risk of death from breast cancer. This could be due to the inhibition of the cytochrome P450 2D6 (CYP2D6) pathway (Kelly et al., 2010).

Another interesting antidepressant is trazodone, a triazolopiridine-derived phenylpiperazine. Trazodone is a potent and selective postsynaptic antagonist of the 5-HT_{2A} receptor as well as a moderate inhibitor of serotinin reuptake (Pansini et al., 1995). It belongs to a class of antidepressants called SARI (serotonin 2A agonist and reuptake inhibitors). Trazodone

shows a high affinity for 5-HT_{2A} receptors, along with a moderate affinity for 5-HT_{1A} receptors. (**Figure 8**)

Paroxetine	doses between 10 and 25 mg/day, with 60-65 % response rates
Venlafaxine	25 or 37,5 mg/day increased to 75 mg/day after 1 week, with response rates of 50-65 %.
Desvenlafaxine	150 mg/day, with response rates of 51-69 %.
Fluoxetine	doses of 20 mg/day, with an effectiveness of about 50%.
Citalopram	20 mg/day, with an effectiveness of about 50%. (Suvanto-Luukkonen et al., 2005; Debra L Barton et al., 2010)
Veralipride	antidopaminergic drug
Sertraline	50 mg/day, with a response rate of 36 % (Kimmick et al., 2006).

Table 1. Dosages and response rates for selected antidepressants

Conversely, a traditional selective serotonin reuptake inhibitor (SSRI), such as fluoxetine, has little affinity for 5-HT_{1A} and 5-HT_{2A} receptors, even though its potency to inhibit serotonin reuptake is greater than that of trazodone. In fact, the concentration of drug needed to produce a 50% inhibition (IC_{50}) of reuptake is only 6 nmol/l for fluoxetine and 115 nmol/l for trazodone (Owens et al., 1997).

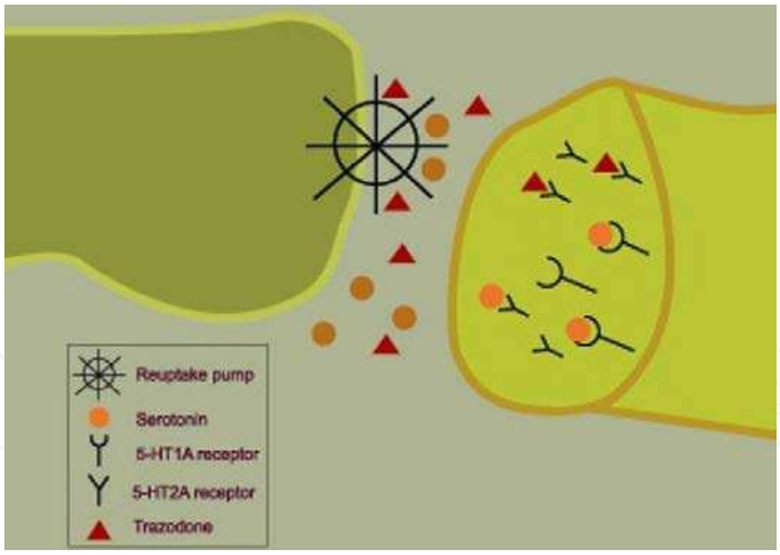

Fig. 8. Trazodone action at synaptic level.

SSRIs stimulate all types of serotonin receptors because they increase free 5-HT levels without blocking any receptors. Although these drugs have been useful in the treatment of depression, they cause adverse reactions, such as agitation, anxiety, and sexual dysfunction, due to the stimulation of 5-HT_{2A} receptors in other tissues (e. g., brainstem and spinal cord) (Stahl, 1998). It is worth noting that 5-HT_{2A} receptors are the main receptors associated with hot flashes and are inhibited by trazodone.

Since trazodone does not cause a clinical blockade of acetylcholine receptors, the potential anticholinergic effects (blurred vision, cardiac alterations, mouth dryness, intestinal disorders, urinary retention, and increased intraocular pressure) are negligible. Moreover, since it lacks any clinical effects on NA inhibition, other potential side effects such as apathy, lack of motivation, anhedonia, and difficulty concentrating are minimal.

Nevertheless, trazodone shows an interesting affinity for α-receptors. The high and moderate activity of trazodone for α_1- and α_2- adrenergic receptors, respectively, might contribute to the beneficial effects described on erectile dysfunction (Krege et al., 2000). On the other hand, this same property could also lead to orthostatic hypotension.

Trazodone also blocks H_1-histamine receptors (H_1) and, probably due to its histamine-blocking properties and potent 5-HT_{2A} antagonist activity (Stahl, 1998; Marek et al., 1992), also exhibits a sedative activity that has been shown to be useful for the treatment of elderly patients with agitation and insomnia.

Because of its pharmacological profile, this antidepressant may be valuable in the treatment of hot flashes in prostate cancer patients undergoing hormone deprivation.

As mentioned above, NA acts on the thermoregulatory center by shortening its response range and lowering its tolerance threshold, which in turn results in cutaneous vasodilation and profuse sweating. Drugs with noradrenergic properties, which could trigger the onset of hot flashes, should thus not be used in prostate cancer patients undergoing hormone deprivation. Furthermore, while NA shortens the thermoregulatory response range, serotonin and dopamine have an opposite effect. (**Figure 6**)

The use of serotonergic antidepressants may be warranted and, in fact, a few of them have already been tested with encouraging results.

In addition, considering that hormone deprivation is associated with low serotonin concentrations and stimulation of 5-HT_{2A} receptors, some drugs, such as trazodone, whose pharmacological profile is characterized by a high affinity for these 5-HT_{2A} receptors and a moderate effect on serotonin reuptake, might be beneficial in the management of hot flashes, unlike serotonergic antidepressants (SSRIs), which lack this property. This profile might also be significantly helpful in the control of anxiety, sleep and erectile dysfunction, all of which would result in a quality of life improvement.

To date there are few studies examining the use of trazodone in hormonally deprived patients. One pilot study assessed the management of hot flashes in 25 menopausal women. No objective effect was seen after doses of 75 mg/day for 3 months, although anxiety, insomnia and irritability were reduced (Pansini et al., 1995). Further studies are required to elucidate the potential efficacy of trazodone against hot flashes by using validated scales to ascertain such effect.

It should be mentioned that the placebo effect can improve hot flashes in 20-40 % of patients, with perceived efficacy rates of 50-75 % for initialuse (J A Sloan et al., 2001; Moyad, 2002).

Other drugs have been shown to be either less effective or ineffective, or have been disregarded for the management of hot flashes because of their high incidence of side effects. (**Table 2**)

Some dietetic measures can be helpful, namely: cold water irrigations or the application of cold; avoiding excessively hot food and very hot environments; limiting the consumption of spicy food, coffee and alcohol; following a diet rich in soy protein-containing products (the use of phytoestrogens, although recommended by some authors, is to be avoided because of its potential effect on hormonal-dependent cancer) (J A Sloan et al., 2001; Carmignani et al., 2010); reducing stress by means of relaxation techniques like yoga ; engaging in non -

strenuous physical exercise to maintain an appropriate weight (being overweight can increase both the frequency and severity of hot flashes) (Sideras & Charles L Loprinzi, 2010; Robert R Freedman, 2005); and quitting smoking.

- Bellergal (phenobarbital + ergotamine + belladonna alkaloids), with a 30 % withdrawal rate from therapy due to toxicity (Bergmans et al., 1987).
- Dietary supplements.
- High-dose supplements of isoflavones/phytoestrogens (both estrogenic and antiestrogenic effects).
- Medicinal plants (Moyad, 2002).
- Vitamin E (Moyad, 2002).
- Methyldopa (M. G. Hammond et al., 1984).
- Relaxation techniques, physical exercise, acupuncture.
- L-Isoleucine and L-Valine (T. Guttuso et al., 2008).

Table 2. Some commonly used measures for hot flash management

Drug or Action	Dosage and Actions	Percentage of Response
Estrogens	Estradiol p.o. (0.25 mg/day) or transdermal (0.05 mg/day)	80-90 %
Progesterones	Megestrol acetate 20 mg/12 h Cyproterone acetate 50-100 mg/day Medroxyprogesterone acetate p.o. 20-40 mg/day or single 400 mg i.m. depot dose	80-90 %
Clonidine	25-400 mcg/day	20-55 %
Antidepressants	Paroxetine 10-25 mg/day Venlafaxine 25-75 mg/day Desvenlafaxine 150 mg/day Fluoxetine 20 mg/day Sertraline 50 mg/day Trazodone 50-150 mg/day	60-65 % 55-65 % 51-69 % 50 % 36 %
Gabapentin	300 mg/8 h	44-60 %
Placebo effect		20-40 %
Others	Bellegard Isoflavones/phytoestrogens Vitamin E Cimifuga Racemosa Acupuncture L-Isoleucine and L-Valine Methyldopa Physical exercise Relaxation techniques	

Table 3. Summary of all data presented

Acupuncture has been studied for alleviation of hot flashes in patients with prostate carcinoma (Harding et al., 2009) and in postmenopausal women (E. M. Walker et al., 2010). However more studies are needed to confirm any benefit (Sideras & Charles L Loprinzi, 2010).
A correlation between body mass index and the frequency of hot flashes, as determined by insulin metabolism in fat tissues and an increase in body temperature, has been shown in recent studies, (Robert R Freedman, 2005; Gold et al., 2000). A relationship has also been reported with tobacco consumption, which might be explained by an effect on estrogen metabolism or a thermogenic action of nicotine, (Robert R Freedman, 2005; Whiteman et al., 2003; Jessen et al., 2003)

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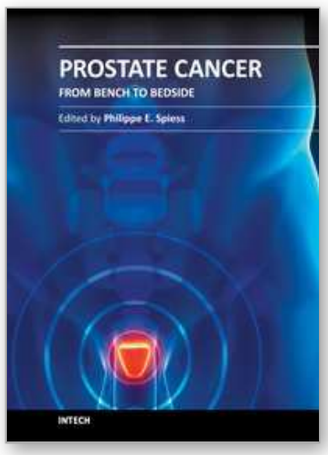

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The present textbook highlights many of the exciting discoveries made in the diagnosis and treatment of prostate cancer over the past decade. International thought leaders have contributed to this effort providing a comprehensive and state-of-the art review of the signaling pathways and genetic alterations essential in prostate cancer. This work provides an essential resource for healthcare professionals and scientists dedicated to this field. This textbook is dedicated to the efforts and advances made by our scientific community, realizing we have much to learn in striving to some day in the not too distant future cure this disease particularly among those with an aggressive tumor biology.

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