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Women dealing with hot flushes: the role of β-alanine

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Abstract. **Hot flushes (HFs) are a very frequent condition in menopausal women, associated with a marked decrease in quality of life, impaired ability to carry on daily activities and sleep disturbances. However, this condition is often only given poor attention in daily practice and in clinical research.**

Indeed, several treatments for HFs exist. The most effective is considered to be hormone replacement therapy, but this strategy has been associated with a poor risk-benefit ratio given its link with the development of cancer. Other treatments have been tested and are currently used, but they are usually only poorly effective or cannot be recommended in all patients due to potential side effects or interference with other molecules. Therefore, there is a major need for new treatment options for HFs.

β-alanine supplementation is widely used for the enhancement of energetic metabolism and is known to be devoid of any relevant adverse effect. BA has also been widely used for the treatment of HFs.

This narrative review will discuss the current pharmacological management of HFs and will present the role of β-alanine in this setting.

Key Words:
Hot flushes, Women's health, Beta-alanine, Supplementation, Hormonal replacement therapy.

Introduction

Menopause is a pivotal life event marked with hormonal and social changes, which heavily impacts on women's health needs. Approximately 25 million women pass through menopause each year. Due to life expectancy increase, the world population of menopausal and postmenopausal women is projected to increase to 1.2 billion by 2030[1]. The menopause transition, which lasts several years, is associated with various symptoms, including vaginal dryness/dyspareunia, urinary frequency, urgency, nocturia, sleep difficulties, adverse mood changes and vasomotor symptoms (VMS)[2,3].

Hot flushes (HFs) are considered one of the most frequent VMS during menopause. HFs consist of a rapid and exaggerated heat dissipation response, characterized by profuse sweating, peripheral vasodilation and feelings of intense internal heat, which quickly spreads across the whole body and face[4-6]. HFs can affect up to 80% of post-menopausal women, and epidemiological data in the USA suggested that VMS are independently associated with multiple cardiovascular risk factors, obesity, lower socioeconomic status, sedentary lifestyle, smoking, premenstrual syndrome, greater bone loss, higher bone turnover and Afro-American ethnicity[7,8].

HFs are long-lasting, with an estimated median duration of symptoms of about 8 years[5-8]. Duration was found to be longer (median: >11.8 years), and post-menopausal persistence to be higher (median: 9.4 years) for women who were premenopausal or early perimenopausal when they first reported frequent VMS. In addition, longer duration was related to younger age, lower educational level, greater perceived stress and symptom sensitivity, and higher depressive symptoms and anxiety at the first report of VMS. Women who were postmenopausal at the onset of VMS had shorter duration of VMS (median: 3.4 years)[8].

The exact pathophysiology of HFs remains poorly understood. However, symptoms of HFs are characterized by impaired peripheral vasodilatory response to lose heat in the hypothalamic thermoneutral zone due to the release of different mediators, including histamine. They may be triggered by small elevations in core body temperature or spicy foods, caffeine and alcohol[9].

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HFs are characterized by transient sensations of heat, sweating, flushing, anxiety, which can last up to 10 minutes, resulting in marked distress, interference in daily activities and impaired sleep quality[5,7,10,11]. The frequency of HF episodes ranges from occasional attacks per week up to even once or twice each hour. Despite their frequency and impact on quality of life, HFs are often neglected by healthcare providers, partly because of their relatively benign nature[7].

Lifestyle interventions are often recommended for the management of HFs, especially in the presence of mild (according to physician's assessment or judgement) symptoms; however, their effectiveness is not consistently demonstrated. On the other hand, pharmacological treatments can be suggested even in case of mild HF and are recommended if the patient is experiencing more severe symptoms[5,7,12]. Remarkably, new treatment options for the management of HFs are eagerly awaited[12].

This review will discuss the current pharmacological management of HF and will present the role of β-alanine (Abufène/Klimalanin, Laboratoires Bouchara-Recordati, Puteaux, France) in this setting.

Pharmacological management of hot flushes: available options and current limitations

Supplementation of systemic estrogen (hormone replacement therapy [HRT]) can be considered the most effective treatment for HFs, since it can lead to a 75% reduction of VMS frequency[5,13]. However, HRT has been associated with an increased risk of breast cancer, especially in combination with estrogen and progestogen, or when the duration is longer than 5 years[14].

A large, double-blind, placebo-controlled study by the Women's Health Initiative (WHI) was conducted in women aged 50-79 years to evaluate the cardioprotective efficacy of HRT. This therapy resulted associated with an increased incidence of breast cancer, compared with placebo, at a follow-up of 5.2 years (hazard ratio [HR]: 1.26; 95% CI: 1.00-1.59)[15]. The study was then stopped early due to the unfavorable risk-benefit ratio of HRT. More recently, a very large (n=58,148) UK cohort study showed a higher risk of developing breast cancer among women on HRT, compared with those who do not use this therapy (HR: 2.74; 95% CI: 2.05-3.65) for a median duration of 5.4 years of use, and this risk increased with duration of HRT (15+ years, HR: 3.27; 95% CI: 1.53-6.99)[16]. A recent meta-analysis confirmed these findings showing that the corresponding risks with 10 years of use starting at the age of 50 years would be about twice as great, in western women. In addition, in past users, excess duration-dependent risks for breast cancer persisted for more than a decade after stopping HRT use[17]. HRT was also related to an increased risk of endometrial cancer. Use of unopposed estrogen, tibolone and sequential estrogen-progestin combined therapy increased the risk of endometrial cancer, while the risk associated with micronized progesterone use is still to be confirmed[18].

According to the above, the current recommendation for the use of HRT is to treat moderate-severe VMS at the lowest possible dose. Moreover, since the findings of the WHI trial were published, the use of HRT for the treatment of HFs decreased by 80%, since both patients and healthcare providers prefer alternative approaches to the management of this condition[19,20].

Other hormonal approaches include high-dose progestin therapy –not nearly as effective as estrogens[21] –or bioidentical hormones sourced by certain plants, which are sustained only by very scant evidence[5]. Non-hormonal therapies include centrally acting drugs such as gabapentin/pregabalin, clonidine, selective serotonin reuptake inhibitors (paroxetine), serotonin-norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine), which are considered more effective than placebo but less effective than HRT[5,7]. Some over-the-counter, non-hormonal therapies include phytotherapic preparations containing soy extract, red clover isoflavones, black cohosh or Chinese herbs, but both their safety and efficacy appear to be modest at best[5,22,23].

On the above-mentioned bases, it appears that no pharmacological treatment for HFs is completely satisfactory. Therefore, there is large room for the evaluation of new therapies[5,7].

β-alanine in the treatment of HFs: pharmacological rationale

β-alanine is a non-essential amino acid, the isomeric compound of the L-alanine (Figure 1). Carnosine, a dipeptide with a high concentration in mammalian skeletal muscle, is synthesized by carnosine synthase from L-histidine and BA, which is the rate-limiting precursor. The chronic oral ingestion of β-alanine has been shown to substantially elevate the carnosine content of human skeletal muscle. Interestingly, muscle carnosine loading leads to improved performance

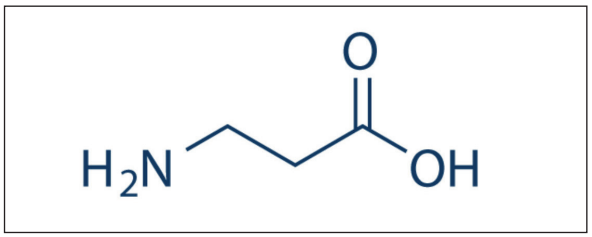

Figure 1. Chemical structure of β-alanine.

in high-intensity exercise in both untrained and trained individuals. Carnosine has an important role in the homeostasis of contracting muscle cells, especially during high rates of anaerobic energy delivery. It may attenuate acidosis by acting as a pH buffer and increase contractile performance by improved excitation-contraction coupling and defense against reactive oxygen species[24]. It has also been suggested that carnosine has an anti-aging activity through multiple mechanisms[25,26]. The use of β-alanine is now a common practice among competitive athletes and in military training, to increase carnitine load and enhance the energetic metabolism by delaying fatigue and promoting recovery[26-31]. According to the International Society of Sports Nutrition, β-alanine is safe in healthy populations at recommended doses; a very rare side effect of high dosage intake is paresthesia (a sort of transient tingling, most often in the extremities of the upper and lower limbs), but this event can be easily managed[29,32].

β-alanine is used for the treatment and prevention of HF and VMS of menopause[33]. Although the precise mechanism of vasomotor response inhibition still requires further investigation, this action seems to be mediated by multiple activities, such as antagonism of nicotinic acid and inhibition of histamine release[34]. In a pharmacological study in guinea pigs, BA 100 or 200 mg/kg was able to protect animals from the peripheral vasodilation induced by nicotinic acid in a dose-dependent manner[35]. Experimental evidence revealed β-alanine can not only exert a long-lasting inhibition of histamine release, but can also activate glycine receptors, modulating both vasodilation and pain sensation[36,37]. Toxicological studies showed that β-alanine exhibits a particularly low acute toxicity (LD_{50} >5.5 g/kg by an intravenous route in mice and LD_{50} >10 g/kg by oral route in mice and rats) and low chronic toxicity (3 months – no abnormality was detected)[35]. These data paved the way for successive clinical experimentations.

β-alanine in the treatment of hot flushes: clinical evidence

The efficacy of β-alanine in the treatment of HFs was first assessed in two studies, which remained unpublished[32]. The former was a placebo-controlled study, conducted in 70 women – 47 of whom with natural menopause and 23 with surgical menopause – who received either β-alanine 400 mg/day or placebo[32]. β-alanine showed superior efficacy of placebo, regardless of the etiology of menopause: β-alanine led to outcomes judged as 'good' or 'very good' effect on hot flushes, by the patient in 70% of cases. In the placebo group, 66% of women underwent treatment failure and 33% obtained a limited improvement. No cases of adverse events directly related to β-alanine were reported. Similar findings were observed in a larger study, again with a placebo-controlled design and involving a total of 100 women (mean age: 49±3 years), 50 of whom received β-alanine (43 in natural menopause and seven in surgical menopause)[32]. At baseline, three patients on β-alanine reported severe symptoms, 19 reported moderate symptoms, and 28 had mild symptoms; after 2 months of treatment, no patient reported severe symptoms, and only eight women had moderate symptoms. Conversely, intensity of symptoms increased in the placebo group. Similar findings were reported in terms of distress associated with HFs (moderate-severe distress was reported in six patients on β-alanine at baseline, and in two patients at 2 months). β-alanine treatment was rated as 'good' (a favorable effect on intensity and tolerability of hot flushes and on distress experienced) by 36 out of 43 treating physicians (84%). No adverse events were reported.

In a published placebo-controlled experience, 26 women in menopause (mean age: 50±5 years) were randomly assigned to β-alanine 400 mg/day and 26 (51±4 years) to placebo for a total of 8 weeks[38]. All women had to have reported at least 10 prior episodes of HFs and were not on any other treatment for HFs. In 56% of cases, patients were in menopause for >27 months, and most of them (90%) were in natural menopause; in the other 44% of cases, patients were in climacteric syndrome. HFs were reported daily in most patients (75%) and were often associated with other symptoms including sleep disturbances, tiredness, irritability, anxiety and sexual dysfunctions. Subjects in the β-alanine group reported a significant decrease in the number of HFs compared to those assigned to placebo, already from week 3 (Figure 2). A higher percentage of patients in the

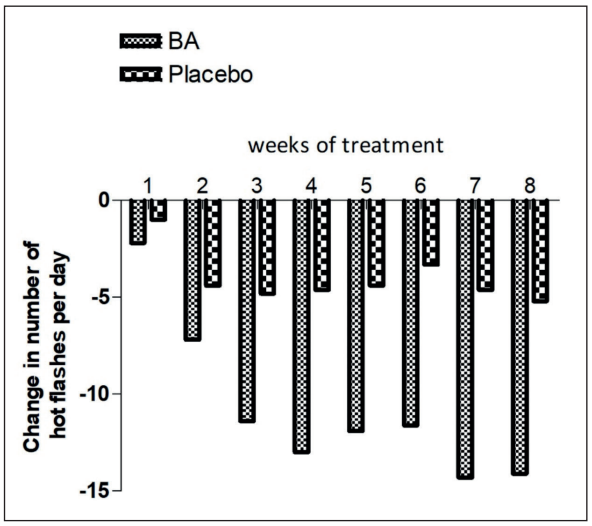

Figure 2. Change in the number of hot flash episodes per day with β-alanine (BA) or placebo in the study by Roueche et al[38]. p=0.02 at week 3 *vs.* placebo, p<0.01 at weeks 4-8 *vs.* placebo.

active treatment group reported no flushes, compared with those in the placebo group, at all measured timepoints. Tolerability of β-alanine was comparable to that of placebo.

More recently, the efficacy of β-alanine in the treatment of HFs was investigated in a number of other studies. In a study by Tatarova et al[34], β-alanine was tested in 108 patients with adenomyosis and grade 3-4 external genital endometriosis. All women were treated for 6 months with triptorelin 3.75 mg intravenous (one injection per month). At month 3, β-alanine treatment (800 mg/day) was started in 78 patients, for a total of 3 further months. Symptoms severity was assessed by the Modified Menopausal Index (MMI)[39]. MMI total score at baseline was 45.8±1.0 In BA recipients – indicative of moderate severity – and 45.9±1.5 in the control group. At 6 months, it decreased to 24.2±0.6, indicative of mild severity, in β-alanine recipients, and persisted at 46.9±1.4 in the control group (p<0.05 active *vs.* control). No changes in serum estradiol were reported. The Authors of that study concluded that β-alanine can be considered the drug of choice in the treatment of neurovegetative symptoms of menopausal syndrome, caused by triptorelin, while it does not affect the blood levels of estrogen.

In another open-label study conducted in 36 patients (mean age: 44±1 years; range 40–57) with more than 10 HFs episodes/day, β-alanine 400 mg/tablet (total dose was variable according to the severity of symptoms) for 12 weeks was able to reduce the number of flushes per day (Figure 3), and was also associated with improvements in other symptoms, including sleep disturbances and tiredness[40]. By the end of the therapeutic course, 30 women (83.3%) reported a complete absence of HFs, in another four (14%) the vasomotor symptoms became weaker and appeared less frequently compared with baseline (Figure 3). Most women reported good tolerability of the medicinal product.

Last, in a randomized, placebo-controlled study conducted in 59 women aged over 45 with surgical menopause, the MMI score decreased from 19.3±2.4 to 9.1±1.5 over a 3-month period of therapy with BA (p≤0.001). Reduction in MMI score was 26%, 45% and 55% higher than those reported with placebo at 1, 2 and 3 months, respectively (p<0.05 for all comparisons) suggesting that the effectiveness of the therapy may increase over time[41]. According to Yurghel et al[33] sublingual administration of β-alanine provided a faster and more intense absorption in comparison with oral administration, producing higher plasma concentrations of the active ingredient.

Discussion

Menopause is a life event involving millions of women every year and heavily impacting on everyday life and on the health condition. VMS are reported by most women for years, starting before menopause and lasting 7-10 years after it. These symptoms are often felt as disabling by affected women but are considered benign and are given only poor attention in daily practice and in clinical research. HFs are the main type of VMS, a very frequent condition in menopausal women, associated with a marked decrease in quality of life, impaired ability to carry on daily activities and sleep disturbances.

Indeed, several treatments for HFs exist. The most effective is considered to be HRT, but this strategy has been associated with a poor risk-benefit ratio given its link with the development of breast cancer. Other treatments have been tested and are currently used, but they are usually only poorly effective or cannot be recommended in any patient due low tolerability or to potential interference with other molecules. There is therefore a major need for new treatment options for HFs.

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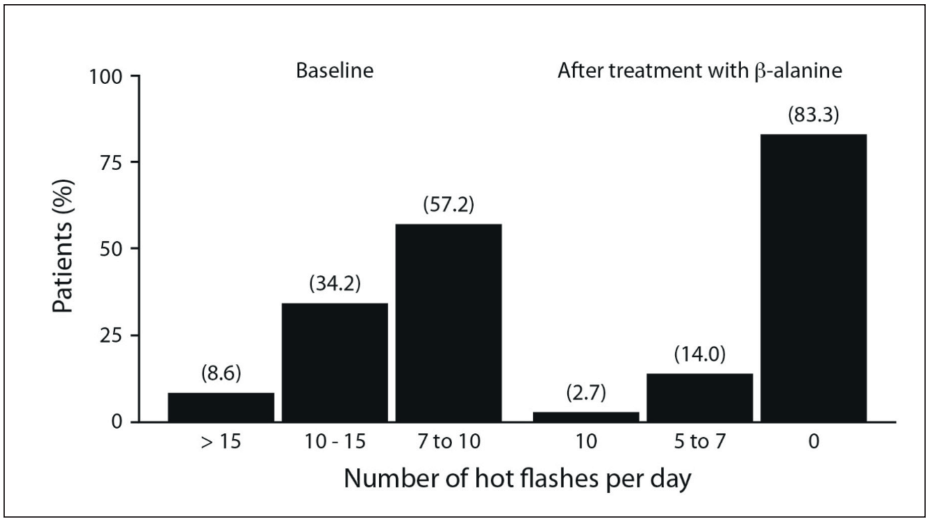

Figure 3. Number of hot flash episodes per day before and after the treatment with β-alanine in the study by Zarochentseva et al[40].

training periods and proved to be devoid of any relevant adverse effect. β-alanine has also been widely used in the treatment of HFs, given its action on vasodilation through inhibition of histamine release, antagonization of nicotinic acid, and activation of glycine receptors. In addition, its role in increasing carnosine load in the muscle may contribute to the general well-being. All studies, although conducted in an overall limited number of patients and without including an active comparator, were consistent in showing a prompt and sustained reduction in the number and intensity of HFs episodes, with a concomitant improvement of quality of life and sleep. These outcomes were achieved regardless of HFs etiology. In fact, efficacy of therapy did not depend on the type of menopause (natural or induced), and the effect of the drug was evident in the entire spectrum of hot flashes severity, i.e., from mild through moderate and to severe case[42]. Tolerability was excellent in all studies, thus lending further support to the use of β-alanine in the treatment of HFs. In addition, as no addiction has been observed, the treatment can be extended on the whole period of vasomotor clinical disorders without limitation of duration[43].

Conclusions

According to the above-mentioned evidence, β-alanine represents a safe and reliable therapeutic option for all women dealing with menopausal hot flushes, especially when HRT is not a suitable choice.

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Conflict of Interests

The authors have nothing to declare.

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