The Potential Role of 5-Hydroxytryptophan for Hot Flash Reduction: A Hypothesis

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Abstract

Hormone replacement therapy (HRT) is contraindicated in women with a history of breast cancer or a high risk of breast cancer development. Recent results from large clinical trials, such as the Women's Health Initiative, have demonstrated increased risks of thromboembolic events and a moderate increased risk of breast cancer in women using conjugated estrogens and progestogens. There is a need for viable non-hormonal alternative treatments to HRT, such as nutritional and botanical therapies, in this population of women, who tend to experience more significant vasomotor symptoms. Safe and effective therapies that do not stimulate breast cell proliferation could prove extremely useful for the management of such symptoms for women in both low- and high-risk breast cancer populations. As a non-hormonal treatment, anti-depressants, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to improve hot flash symptoms in women. The proposed mechanism is related to an increase in serotonin allowing for an increase in the set point of the brain's thermoregulator. In small clinical studies, the administration of tryptophan and 5-hydroxytryptophan (5HTP), the precursors of serotonin, have been shown to reduce depressive symptoms, possibly by enhancing the synthesis of serotonin. Thus, increased serotonin levels may have the ability to decrease hot flashes in a mechanism similar to that of SSRIs without the risks of breast cell stimulation. This would be particularly desirable for menopausal women with breast cancer or with risks of breast cancer. This article discusses the background information on hot flashes, SSRIs, tryptophan, and 5HTP, and possible clinical application of 5HTP for menopausal women with breast cancer risk. (*Altern Med Rev* 2005;10(3):216-221)

Introduction

At menopause a woman's ability to produce her own endogenous hormones is greatly reduced. Menopause is recognized by the cessation of menses for at least one year and, although it is not a disease, the transition into menopause is often accompanied by symptoms. While the etiology of these symptoms is not completely understood, they can affect women both physically and psychologically, and can vary in frequency as well as intensity.[1] The most common symptoms include hot flashes, mood changes, depression, cognitive changes, vaginal dryness, decreased libido, dyspareunia, decreased energy, sleep disturbances, and weight gain.

Hot flashes are the hallmark symptom of estrogen fluctuation, which occurs during the menopausal transition. A hot flash is generally characterized by a sudden sensation of intense body heat, often with profuse sweating of the head, neck, and chest. Hot flashes often occur at night, lasting several seconds to minutes, and can result in significant sleep deprivation. Hot flashes may be accompanied by heart

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Table 1. Main Outcomes of Four-week Anti-depressant Studies on Hot Flash Reduction

Investigator	N	Intervention	Study Design	Main Outcomes at Week 4
Loprinzi [10]	24	12.5 mg daily oral venlafaxine	Pilot Evaluation	58% patients > 50% reduction in HFS*
Loprinzi [11]	191	placebo or 37.5 mg, 75 mg, or 150 mg daily oral venlafaxine	RCT	27%, 37%, 61%, and 61% reduction in HFS in four groups, respectively
Loprinzi [12]	68	placebo or 20 mg daily oral fluoxetine	Crossover RCT	50% reduction in HFS in treatment arm vs. 36% in placebo arm
Perez [14]	16	dose escalated to 15 mg and 30 mg daily oral mirtazapine	Pilot Evaluation	52.5% and 59.5% reduction in HFS, respectively
Barton [13]	17	dose escalated to 20 mg daily oral citalopram	Pilot Evaluation	64% reduction in HFS

* HFS=Hot flash scores
RCT=Randomized controlled trial
N=number of subjects

palpitations, anxiety, irritability, and panic. Although not life threatening, hot flashes can significantly impact a woman's quality of life, functional ability, sexuality, and self-image.[2,3]

HRT has been the mainstay of treatment for menopausal symptoms. The options include estrogen replacement therapy (ET) alone in women who have undergone hysterectomy or estrogen and progestogen replacement therapy (EPT) in women with an intact uterus. The estrogens often prescribed and examined in larger clinical trials are conjugated estrogens and come from an equine source. Progesterone or progestogen, which include synthetically derived progestins such as medroxyprogesterone acetate (MPA), and natural progesterone such as oral micronized progesterone, are administered to counteract estrogen's proliferative effect on the uterus.[4] The addition of progestogens to the estrogen regimen for hormone replacement may be associated with patient inconvenience as they can produce the undesirable effect of vaginal bleeding and premenstrual symptoms when a cyclic regimen of these hormones is used.[5] A recent study performed by the Women's Health Initiative (WHI) suggests that women receiving HRT in the form of Prempro®, a combination of conjugated equine estrogens and MPA, are at an increased risk for stroke and a moderate increased risk of breast cancer.[6] In the mouse, progestin plus estrogen was found to be more mitogenic in the adult mammary gland than estrogen alone.[7] Estrogen plus progesterone replacement therapy also substantially increases the percentage of women with abnormal mammograms due to increased breast density, suggesting that estrogen plus progesterone may stimulate breast cancer growth and hinder breast cancer diagnosis.[7]

Menopausal Symptoms in Breast Cancer Patients

Breast cancer survivors may experience menopausal symptoms due to a variety of reasons. Newly diagnosed, postmenopausal breast cancer patients are counseled to stop any hormone replacement therapy. The abrupt discontinuation of estrogen therapy usually results in a return of menopausal symptoms. Many newly diagnosed, premenopausal breast cancer patients undergo premature menopause secondary to chemotherapy or therapeutic ovarian ablation. Tamoxifen also produces or enhances menopausal symptoms.[8] It has been reported that menopausal symptoms may be more severe in some breast cancer patients compared with healthy women experiencing natural menopause.[9] In addition, decreased physical and emotional quality of life in breast cancer survivors has been correlated with a higher prevalence and severity of menopausal symptoms, particularly hot flashes.[9]

Anti-depressants for Hot Flashes

Anti-depressants such as SSRIs are currently being used as a treatment option for women with hot flashes when estrogen replacement is contraindicated (Table 1). The efficacy of anti-depressants for the treatment of menopausal hot flashes has been demonstrated in phase III trials.[10,11] Venlafaxine was evaluated at three different doses in a randomized, double-blind, crossover design. Daily oral intake of 37.5 mg, 75 mg, 150 mg, or placebo, resulted in a significant reduction of hot flashes compared to placebo at all dose levels, with the most efficacy observed with the 75- and 150-mg doses (61% reduction in both groups).[11] A similar trial was performed evaluating fluoxetine at 20 mg daily compared to placebo.[12] A 50-percent reduction in hot flashes was observed compared to 36 percent for placebo (p=0.02). Similar trials examining the effects of other anti-depressants, such as citalopram and mirtazapine, have also demonstrated a reduction in hot flashes.[13,14] However, anti-depressant drugs such as SSRIs are not without side effects and therefore may not be an ideal therapeutic intervention. Common bothersome side effects include insomnia, somnolence, nausea, vomiting, anorexia, and decreased libido.[15,16]

Physiology of Hot Flashes

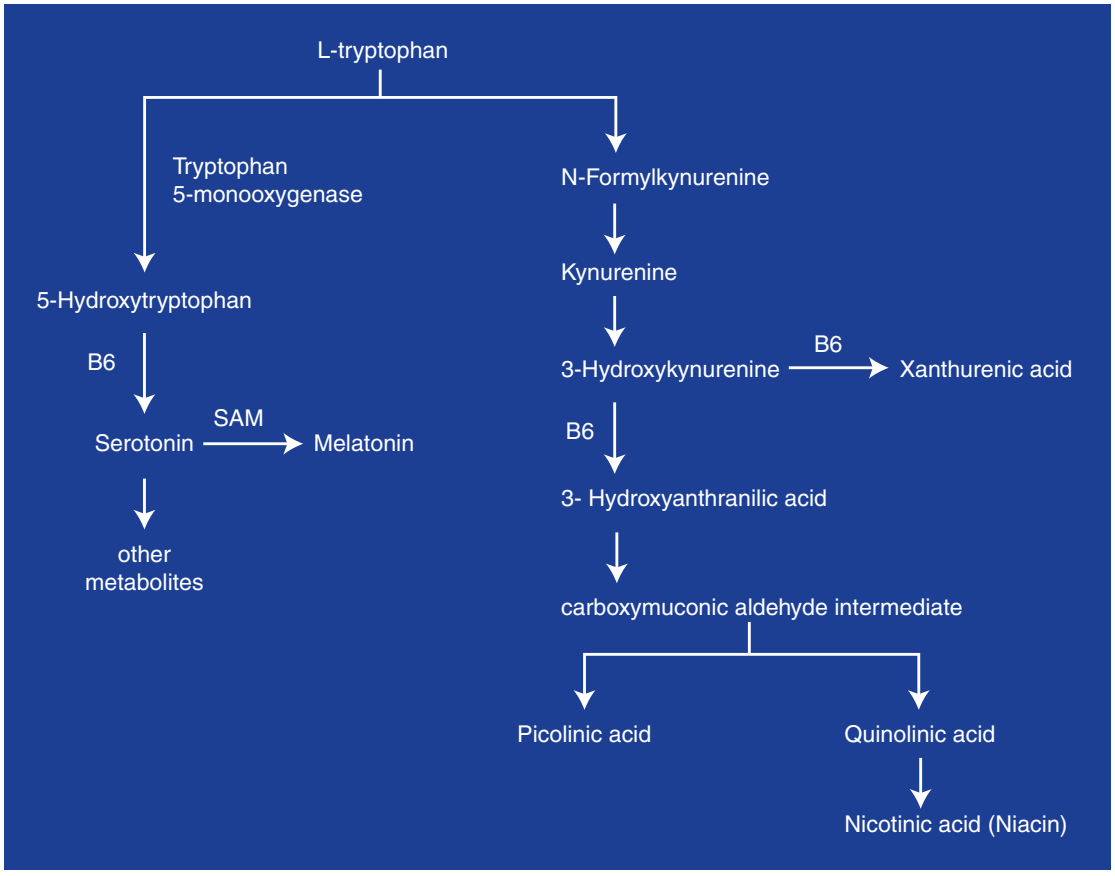
Although anti-depressant medications have demonstrated efficacy, the exact mechanism of action remains unknown. One of the theories of hot flash physiology is that a reduction in endorphin production decreases the set point of the thermoregulatory center in the hypothalamus. A reduction in the thermoregulatory set point will lead to heat loss, resulting in a hot flash as the body attempts to maintain a temperature within the set point.[17] It has been postulated that norepinephrine levels are directly correlated with this reduction in the thermoregulatory set point.[18] Studies have demonstrated an increase in norepinephrine levels in the brain both prior to and during a hot flash.[17,19] Estrogen enhances the synthesis of serotonin and endorphins,[17,19,20] and serotonin and endorphins are believed to inhibit the production of norepinephrine.[17]

According to one hot flash model, estrogen withdrawal leads to decreased blood levels of endorphins and serotonin and an increase in serotonin receptors,[18,21] resulting in a loss in the feedback inhibition of norepinephrine production and a reduction in the thermoregulatory set point.[17,18] Thus, agents that increase estrogen, serotonin, and endorphin levels or that decrease central norepinephrine release would be expected to reduce hot flashes.[17,21] SSRIs block serotonin receptor subtype 2a and stimulate receptor subtype 1a, thereby increasing serotonin levels. This prevents hyperthermia and inhibits hypothermia,[18,20] providing a potential mechanism by which SSRIs reduce hot flashes. Maintaining serotonin levels would attenuate the rise in norepinephrine associated with hot flashes.

Tryptophan and 5-Hydroxytryptophan (5HTP): Serotonin Precursors

Tryptophan is the amino acid precursor of serotonin. The amount of tryptophan that can be shunted into serotonin production is dependent on many variables, including the amount of niacin present and the availability of the substrate. Only free plasma tryptophan can cross the blood brain barrier via a carrier protein to enter the central nervous system (CNS). Once in the CNS, tryptophan is converted to 5HTP and then is decarboxylated to serotonin (Figure 1).[22] The levels, and possibly function, of several

Figure 1. Pathway of Tryptophan Metabolism



neurotransmitters can be influenced by the supply of their dietary precursors.[23] A reduction in tryptophan has been correlated to a reduction in serotonin.[24] Tryptophan increases serotonin synthesis in the brain and may stimulate serotonin release.[25]

5HTP and other Serotonin Precursors as Substitutes for Anti-depressant Medications

Altering the metabolism of and biotransformation processes for serotonin may be an important feature for the treatment of depression.[26] Meta-analyses and reviews of both 5HTP and tryptophan suggest there is clinical benefit in the administration of these serotonin precursors for the treatment of depression.[27] Tryptophan has been shown to be useful in mild depression with bipolar disorder resistant to pharmacological treatment and to enhance the effect of other anti-depressant drugs.[22] Tryptophan has also demonstrated efficacy in the treatment of premenstrual dysphoric disorder (PMDD).[28] PMDD is a specific disorder associated with a cluster of symptoms, including sadness, hopelessness, self-deprecation, tension, anxiety, emotional lability, tearfulness, anger, and irritability, that are present in the last luteal week and resolve with menses onset. The magnitude of the reduction of symptoms from baseline in maximum luteal phase was 34.5 percent with tryptophan compared to 10.4 percent with placebo.[28]

A review of 15 clinical trials using 5HTP, in dosages ranging from 50-800 mg for depression, demonstrated improvement of depressive symptoms by 56 percent.[29] Observational studies and a few randomized trials have demonstrated that 5HTP and tryptophan both have therapeutic value in patients

with mild or moderate depression[30] with few adverse effects.[26] Although the studies are few, the evidence suggests that treatment with either tryptophan or 5HTP is better than placebo for depression.[31,32] While there are unconfirmed reports that the use of 5HTP may be associated with some side effects such as headache, nausea, drowsiness and lightheadedness, 5HTP is generally considered a safe dietary supplement.

Rationale for using 5HTP for Hot Flashes

Anti-depressants have been shown to improve hot flash symptoms in women with breast cancer or an increased risk of breast cancer, although as noted the exact mechanism is unknown.[10,11,13,14] Given the current understanding of hot flash physiology, the mechanism is likely due to increased serotonin and endorphin production, thereby increasing the set point of the brain's thermoregulator. Clinical trials of 5HTP for depression and related disorders show that the mechanism for improvements in symptoms may be due to an increase in serotonin levels. Theoretically 5HTP supplementation would have the ability to increase the amount of serotonin available, thus producing a similar effect to the SSRIs without the potential drawbacks. To date there are no direct comparative studies available to support this theory.

Conclusion

There is a growing need for alternatives to HRT for hot flashes, especially in at-risk breast cancer populations where HRT is contraindicated. Due to inconclusive findings, the evidence thus far on 5HTP and depression limits its use to patients with mild depression who are contraindicated to take antidepressant drugs.[27] Considering the biochemical theoretical impact of 5HTP on serotonin levels and subsequent thermoregulator centers and the lack of adverse events reported, the use of 5HTP for hot flashes poses an interesting hypothesis that warrants investigation. Agents that modulate neurotransmitters should be explored to not only evaluate the clinical significance of use for women experiencing debilitating symptoms that reduce their quality of life, but also to better understand the causes of hot flashes. Scientific insight into serotonin and endorphins in hot flashes could provide innovative management of menopausal symptoms and a possible new armamentarium of treatments that do not include hormone replacement therapy, which has demonstrated morbidity and mortality. While 5HTP is generally considered safe,[33] until adequately powered efficacy and safety studies with a large sample size and randomized controlled trials are conducted in menopausal women, recommendation of 5HTP for hot flashes can not be substantiated at this time. Evidence of safety, including dose-response studies, is needed to consider this non-hormonal alternative for women with risk of breast cancer.

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