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Venlafaxine alters microvascular perfusion, [^{123}I]-beta-CIT binding and BDI scores in flushing postmenopausal women

Jenifer Sassarini[a,*], Rajeev Krishnadas[b], Jonathan Cavanagh[b], Alice Nicol[c], Sally L. Pimlott[d], William Ferrell[e], Mary Ann Lumsden[a]

[a] Obstetrics and Gynaecology, School of Medicine, College of Medical, Veterinary and Life Sciences, University of Glasgow, G11 6NT, United Kingdom
[b] Sackler Institute of Psychobiological Research, Institute of Health and Wellbeing, Southern General Hospital, Glasgow G51 4TF, United Kingdom
[c] Nuclear Medicine Department, South Glasgow, NHS Greater Glasgow and Clyde, United Kingdom
[d] West of Scotland Radionuclide Dispensary, University of Glasgow and Greater Glasgow and Clyde NHS Trust, Glasgow G11 6NT, United Kingdom
[e] Institute of Infection, Immunity and Inflammation, University of Glasgow, G11 6NT, United Kingdom

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ABSTRACT

Background: Although 70% of postmenopausal women suffer from hot flashes the pathophysiology is poorly understood. The serotonin and noradrenaline reuptake inhibitor (SNRI) venlafaxine provides relief of flushing although the mechanism is unknown and could involve a central effect and/or a peripheral effect. Using single photon emission computed tomography (SPECT) we studied the central serotonin transporter (SERT) in vivo using [^{123}I]-beta-carbomethoxy-3-β-(4-iodophenyl)tropane (beta-CIT) and, as previous studies have shown that reactivity of the skin blood vessels is enhanced in those who flush, we examined cutaneous microvascular perfusion.

Methods: Cutaneous microvascular perfusion was assessed in 31 postmenopausal women, with flushing, using laser Doppler imaging with iontophoresis (LDI + ION), before and after 8 weeks of treatment with venlafaxine. A sub-group of 14 of these women also had SPECT imaging at both time points to evaluate the availability of SERT in the brain. Flush frequency and score was recorded, and Beck Depression Inventory (BDI) II scores were assessed before and after treatment.

Results: Following treatment with venlafaxine, there was a significant reduction in the [^{123}I]-beta-CIT binding ratio, BDI scores, flushing and endothelial dependent perfusion response. [^{123}I]-Beta-CIT reduction was associated with BDI reduction ($r^2 = 0.54$; $F = 8.8$; $p = 0.004$), but not flushing reduction or perfusion reduction.

Conclusions: Venlafaxine resulted in a decrease in BDI II scores with an associated reduction in [^{123}I]-beta-CIT binding in a group of non-depressed women. It also improved flush frequency and severity which may be as a result of decreases seen in enhanced cutaneous microvascular perfusion.

1. Introduction

It is well known that a significant proportion (73%) [1] of women experience vasomotor symptoms at the time of, and for anything up to 20 years (20%) following, the menopause [2]. It is more common for these symptoms to be self limiting and to resolve within 2–5 years, however during this time they have an, often profoundly, negative effect on quality of life and 25% of women have reported considerable morbidity associated with these. Yet, despite the impact that this has on some 1.2 million women in the UK, we still have a limited understanding of hot flashes.

A hypothalamic mechanism underlying their pathophysiology has been proposed by Freedman et al. studies, by is group, using an ultrasensitive temperature probe suggest that hot flashes are triggered by small elevations in core body temperature (T_c) acting within a narrowed thermoneutral zone in symptomatic postmenopausal women [3]. This group found that small but significant elevations in T_c precede most (76%) hot flush episodes [3–5]. These same investigators subsequently found that postmenopausal women with hot flashes had a narrower thermoregulatory zone

Abbreviations: SSRI, specific serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; SERT, serotonin transporter; BDI, Beck's Depression Inventory; 5HT, serotonin; MPOA, medial preoptic area of the hypothalamus; [^{123}I]-beta-CIT, [^{123}I]-beta-carbomethoxy-3-β-(4-iodophenyl)tropane; ACh-AUC, acetylcholine-area under the curve; SNP-AUC, sodium nitroprusside-area under the curve; HFRDIS, hot flush related daily interference score; NTA, night time awakening; LDI + ION, laser Doppler imaging with iontophoresis.

* Corresponding author at: University of Glasgow, Level 2 McGregor Building, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, United Kingdom.
Tel.: +44 141 2112914; fax: +44 141 2112012.
E-mail address: jenifer.sassarini@glasgow.ac.uk (J. Sassarini).

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(0 °C) compared with postmenopausal women who do not flush (0.4 °C) and that this narrowing was mainly due to a lowering of the sweating threshold in symptomatic women [6]. This dysfunction in thermoregulation may lie within the control centre, as suggested by Freedman, the medial preoptic area of the hypothalamus (MPOA), however it is also possible that there may be underlying pathology in the messengers (adrenergic neurones controlling vasoconstriction and cholinergic neurones controlling vasodilatation) and/or the effectors (cutaneous vessels). It has been shown that flushing women have a diminished vasoconstrictor response to cold [7] and that they have increased blood flow to the forearm and hand during a flushing episode [8].

Therefore, if a hot flush is considered to be an unregulated or unwarranted heat dissipation response, both being characterised by sweating and peripheral vasodilatation, what is the trigger, and what is the mechanism?

Noradrenaline is thought to play a key role in lowering the thermoregulatory set point and triggering hot flashes [6,9] and we have recently examined the role of the α-adrenergic system on cutaneous vascular reactivity in postmenopausal women with flashes. While changes in both perfusion and clinical flushing responses were observed in this study, definitive conclusions were difficult to draw as a result of a significant placebo effect [10].

Oestrogen is likely involved as these changes occur at times of relative oestrogen withdrawal, however, there is little correlation between hot flashes and circulating oestrogen levels [11,12].

Serotonin or 5-hydroxytriptamine (5-HT) is involved in many bodily functions including mood, anxiety, sleep, sexual behaviour and eating, and thermoregulation [13]. Oestrogen withdrawal is associated with decreased blood serotonin levels, returning to normal with oestrogen therapy [14,15], although the mechanism for this is unknown. In addition, short-term oestrogen therapy has been shown to bring about a significant increase in 5-HT_{2A} receptor binding in the higher centres of the forebrain in both animal studies and in postmenopausal women [16,17]. Furthermore, selective serotonin reuptake inhibitors (SSRI), designed to increase the available serotonin at the serotonergic synapse, have been shown in placebo-controlled trials to be effective in reducing the number and severity of hot flashes [18]. Venlafaxine, too, has been found to be effective in reducing flushing [19] and although it is a serotonin and noradrenaline reuptake inhibitor, at low doses it probably acts as an SSRI [20].

Serotonin exhibits strong vasoactive properties [21], possibly through stimulation of 5-HT receptors on endothelial cells [22]. A hot flush resembles a heat loss mechanism, with peripheral vasodilatation and sweating, and we have previously shown that peripheral cutaneous vascular responses to vasoactive substances are increased in postmenopausal women with severe flushing [23]. We therefore aimed to assess the role of serotonin in flushing and the mechanism whereby venlafaxine improves vasomotor symptoms peripherally by examining cutaneous microvascular perfusion.

Furthermore, sympathetic control of the cutaneous vascular bed during a febrile reaction, often accompanied by sweating, occurs via a pathway descending from the hypothalamus and basal forebrain to the spinal cord [24]. Dysfunction here would be in keeping with Freeman's hypothesis. Animal studies have also demonstrated that activation of inhibitory 5-HT1A receptors have been shown to cause a fall in body temperature associated with dilation of the cutaneous vascular bed [25].

It is possible to study the serotonin transporter (SERT) in vivo in the human brain by using radioligands that bind to SERT in combination with single photon emission computed tomography (SPECT). The iodine-labelled radioligand [^{123}I]-beta-CIT has a high affinity for SERT [26]. We will examine the relationship between SERT and the effect of venlafaxine on both flashes and peripheral vasoreactivity.

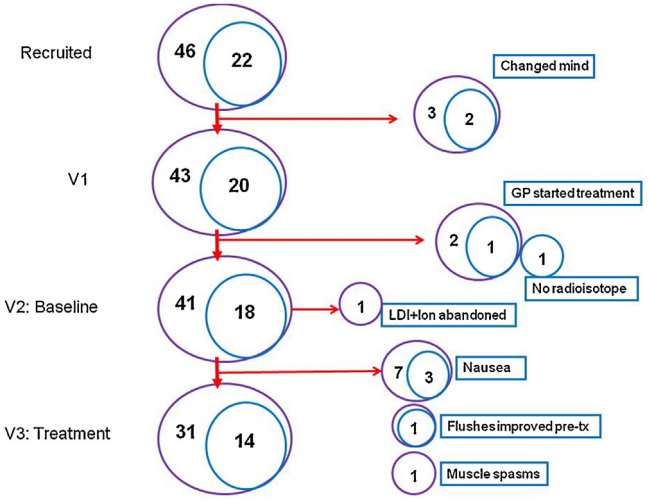

Fig. 1. Study design. Figure illustrating longitudinal study design with numbers of participants in LDI + ION (purple circle) group and SPECT (blue circle) subgroup. Numbers of withdrawals with reasons (same colour-code) illustrated. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

2. Methods

2.1. Study design

Forty six postmenopausal women aged 45–65 years, who were non-smokers, non-hypertensive, non-diabetic and not taking any drugs which could affect vascular function were recruited into the study through Scottish media coverage, from gynaecology and menopause clinics and the West of Scotland Breast screening centre in Glasgow. Menopausal status was determined by amenorrhoea for 1 year or longer. Only two participants had amenorrhoea less than 1 year, and in both FSH was greater than 40. Those currently taking antidepressant medication or hormone replacement therapy were excluded. The study was conducted in accordance with the Declaration of Helsinki with institutional ethics committee approval (REC 09/MRE00/40). All patients gave written informed consent.

The study had a longitudinal design (Fig. 1). At visit 1 (V1), consent was obtained and baseline questionnaires were completed. At visit 2 (V2), baseline cutaneous microvascular perfusion was assessed using laser Doppler imaging with iontophoresis (LDI + ION), and participants returned for repeat assessment at V3 following 8 weeks of treatment with venlafaxine 37.5 mg twice daily. Each participant was asked to keep a hot flush diary for 4 weeks prior to initial assessment and throughout the study. Depression was rated using the BDI scale. Following recruitment, 3 women declined continued participation in the study. Following V1, a further 2 were excluded as a result of therapy commenced by their primary care physician. One assessment had to be abandoned at V2, secondary to vasovagal attack and a further 9 participants were lost prior to V3. Seven of the nine were due to nausea, 1 participant reported 'muscle spasms', and 1 reported that her flashes had improved since initial assessment and therefore declined treatment. We therefore report the results from 31 participants who completed LDI + ION examination at both time points.

We recruited 22 of these women to undergo SPECT scanning in addition to LDI + ION. 4 withdrew prior to baseline assessment and 4 withdrew during the treatment period and prior to second