Sigma’s 30th International Nursing Research Congress

Brain Bioenergetics, Cognitive Activity, and Menopausal Vasomotor Symptoms

Sharon Dormire, PhD, RN
College of Nursing, Texas A&M University, Bryan, TX, USA

Purpose:

Menopause is a sex-specific risk factor for Alzheimer’s Disease (AD); specifically, the Alzheimer’s Association reports that of the 5.3 million Americans with AD, 3.3 million are women and only 2.0 million are men. The physiologic basis for this sex difference is unknown. Although menopausal hot flashes (HF) have long been assumed to be benign, albeit uncomfortable, emerging evidence links higher rates of HF with both cognitive decline and cardiac disease. HF are experienced by 80% of menopausal women in the US. The underlying mechanism or symptom experiences that differentiate women at risk for or predict sequelae is not known. Understanding HF physiology is critical to reducing their negative impact on symptomatic women, preventing cognitive and cardiac sequelae, and developing relevant interventions.

Building on studies of the neuroprotective effects of estrogen we have tested the Impaired Glucose Delivery Model of Vasomotor Symptoms. Neuronal activation stimulates neurobarrier coupling to supply glucose; the coupling process both increases production of glucose transporter 1 (GLUT 1) and vasodilation at the blood brain barrier. With estrogen decline at menopause, we hypothesize that the GLUT 1 response is diminished and the neurovascular response overcompensates resulting in the HF. Based on this model, the principal investigator (PI) conducted a series of experimental studies demonstrating HF decrease with glucose administration. We found that HF were associated with lower blood glucose levels (less than 100 mg/dL) and were significantly reduced when blood glucose was higher, supporting the research hypothesis.

Based on our hypothesis, we propose that cognitive activity would stimulate HF by increasing brain glucose demands. The purpose of this study is to first validate the efficacy of a protocol to reliability stimulate VMS through cognitive activity so that we could subsequently image dynamic bioenergetics in the brain during vasomotor symptoms using functional magnetic resonance imaging.

Methods:

To achieve the first aim, a time-series design study using four standardized cognitive challenge tests was developed. After Institutional Review Board approval, a sample of postmenopausal women age 45 to 65 experiencing 7 or more VMS per day was recruited. After completing the informed consent process and demographic data, each participant was oriented to both the Bahr Skin Conductance monitor for VMS and the FreeStyle Libre Pro for continuous blood glucose assessment and the monitors applied. These observational data were the first to provide continuous longitudinal assessment of VMS and blood glucose in the ambulatory setting as women conduct their activities of daily living. However, this data is not the focus of this presentation.

On the fifth day of observational assessment, participants were scheduled for the experimental cognitive activation of VMS experiment; participants were instructed to fast for a period of at least four hours before the scheduled experiment. Participants were first oriented to the research conditions and computer tests before questions were answered. Four computer-based cognitive tests were administered in random order each for a period of five minutes with a 3-minute rest period between each administration. Upon completion of the cognitive tests and related rest periods, each participant was fed a standard light meal, compensated for their participation, and the imaging study explained before the VMS and blood glucose monitors were removed.
For the second aim of this study women consenting to participate in the imaging study used RedCap to complete the standard risk assessment from used for all Magnetic Resonance Imaging at the collaborating agency conducting the fMRIs. The collaborating radiologist reviewed all risk assessment forms and collaborated with the research team to clarify any concerning information. On the scheduled date of the fMRI, participants were asked to fast for a minimum of four hours before the scheduled procedure. Upon arrival at the imaging center, fasting status was confirmed through a blood glucose test conducted via finger stick. Functional magnetic resonance imaging (fMRI) was performed on a Siemens Magnetom 3T Verio scanner. Localizer and structural T1-weighted images were first obtained. These were followed by echo-planar blood oxygen level dependent (EPI-BOLD) sequences. A total of 4 testing scans, during administration of the same psychological testing used in the cognitive stimulation of VMS phase of this study. The participants indicated the start and end of a hot flash sensation by pressing on a squeeze ball, and the times were noted. Blood glucose was evaluated upon completion of the fMRI sequences and the participant fed a standard meal.

Results:

Thirty-six women were recruited for this study. Several women were lost to the study due to difficulty scheduling for either monitor application or the psychology testing within five days, three were unresponsive after initial verbal consent to participate, and four were lost to analysis due to incomplete data. The resulting sample was twenty-seven postmenopausal women symptomatic for vasomotor symptoms in the cognitive stimulation of VMS phase. Cognitive stimulus of VMS data were analyzed using linear regression. Cognitive activity stimulated VMS in 26.06 minutes for 90.9% of participants. VMS was not related to difficulty of cognitive stimulus but was related to time in the testing conditions.

In the imaging phase of this study women with claustrophobia, metal used in surgical treatments, or physical limitations to lying on the MRI bed were excluded. As a result, nineteen women completed the imaging phase. Not all women experienced VMS during the imaging study and several were excluded due to short duration of VMS (< 20 seconds) precluding effective imaging. Of the final sample significant changes in bioenergetics (specifically activation) was noted in the anterior cingulate cortex and the corpus callosum.

Conclusion:

Advanced in technology now allow for collection of high-quality longitudinal VMS and blood glucose data. Cognitive activity can effectively stimulate VMS under fasting conditions in the laboratory setting, providing additional support for the Impaired Glucose Delivery Model of Vasomotor Symptoms. Further evaluation of the efficacy of cognitive stimulus for VMS is needed using a cross-over design comparing fasting and postprandial conditions. Additional study is also needed to examine the characteristics differentiating women who experienced VMS from those who did not. Finally, our preliminary data indicate that bioenergetic changes in the brain are evident as women experience VMS. Additional study is to: evaluate the longitudinal effect of these changes, examine the impact of stage of reproductive aging (STRAW +10) on bioenergetics both at rest and during VMS, and compare these bioenergetics in samples of symptomatic and non-symptomatic postmenopausal women.

Title:
Brain Bioenergetics, Cognitive Activity, and Menopausal Vasomotor Symptoms

Keywords:
Cognitive Health, Menopause and Vasomotor Symptoms
References:


Abstract Summary:
The relationship between menopausal changes in brain bioenergetics, cognitive activity, and vasomotor symptoms (VMS) will be detailed. VMS were effectively stimulated in symptomatic women through cognitive activity. Activation of the anterior cingulate nucleus and corpus callosum was noted during VMS with functional MRI. Implications will be discussed.

Content Outline:
A. Introduction

1. Although menopausal vasomotor symptoms (VMS) have long been assumed to be benign, albeit uncomfortable, emerging evidence links higher rates of VMS with both cognitive decline and cardiac disease.
2. VMS are experienced by 80% of menopausal women in the US.
3. The underlying mechanism or symptom experiences that differentiate women at risk for or predict sequela is not known.
4. Understanding VMS physiology is critical to reducing their negative impact on symptomatic women, preventing cognitive and cardiac sequela, and developing relevant interventions.
B. Learning Outcomes and Related Content

1. Describe neurobarrier, neurometabolic, and neurovascular coupling as bioenergetic processes of glucose regulation in the central nervous system.
   1. Activation of CNS neurons from resting states generates both increased glucose consumption in the brain and glucose transport at the blood brain barrier since glucose is not stored.
   2. Neuron activation leads a neurovascular coupling response to increases in blood vessel diameter and blood flow to provide adequate blood supply to meet the nutrient needs.

2. Link neurobarrier coupling, blood glucose, and vasomotor symptoms through the Impaired Glucose Delivery Model of Vasomotor Symptoms
   1. Neurobarrier coupling then upregulates GLUT 1, a carrier protein for facilitated diffusion in the endothelial cells of the blood brain barrier. This process, however, is estrogen dependent: estrogen augments GLUT 1 in the cerebral cortex, enabling rapid response to changing glucose needs that are associated with brain activation.
   2. In an effort to keep brain glucose levels stable, GLUT 1 responds to glucose concentrations in the blood with down-regulation during periods of increased glucose concentrations, and with enhanced production in response to glucose decline.
   3. As estrogen declines during the menopausal transition, neurobarrier coupling with upregulation of GLUT 1 is limited and the hot flash is proposed to be the result of an exaggerated response of the neurovascular coupling system.
   4. To evaluate this relationship, a diverse sample of 27 postmenopausal women symptomatic for VMS was recruited for an observational study. The relationship between fluctuations in blood glucose (FreeStyle Libre Pro) and VMS (Bahr Skin Conductance Monitor) for 5 consecutive days.

3. Explain the effect cognitive activity on VMS in symptomatic menopausal women.
   1. Menopause is a sex-specific risk factor for Alzheimer’s Disease (AD).
   2. 5.3 million Americans with AD, 3.3 million are women and only 2.0 million are men.
   3. The physiologic basis for this sex difference is unknown.
   4. While monitoring for blood glucose and VMS, a time-series design was used to evaluate the theoretical premise that cognitive activity is an effective stimulus for VMS in a sample of 27 symptomatic women. Four cognitive activities were tested in random order.

4. List areas of metabolic change in the brain during VMS compared to baseline in symptomatic women.
   1. Brain imaging studies in women with VMS have demonstrated hypometabolism and mitochondrial changes similar to those observed in AD.
   2. Estrogen-related changes in brain glucose transport and metabolism resulting in VMS may be the link with postmenopausal risk for AD.
   3. The cognitive stimulus set was used during function MRI to evaluate changes in brain bioenergetics during menopausal VMS in a sample of 19 symptomatic women.

C. Results

1. Menopausal vasomotor symptoms patterns were related to blood glucose in the ambulatory setting.
2. Cognitive activity effectively and reliably stimulated VMS in the laboratory setting.
3. Areas of metabolic activation were identified using fMRI during VMS inducted by cognitively activity.

First Primary Presenting Author
Primary Presenting Author
Author Summary: Dr. Dormire has more than 40 years of experience in women’s health nursing. She is known as an expert educator in maternal-newborn nursing and nursing research as evidenced by numerous teaching awards. Her scholarship focuses on women’s reproductive issues related to pregnancy and menopause. Dr. Dormire’s research led to the development of the Impaired Glucose Delivery Model of Vasomotor Symptoms. Her work has been disseminated in a range of research publications and presentations.