BRIEF REPORT

Menopausal Hot Flash Frequency Changes in Response to Experimental Manipulation of Blood Glucose

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- ***Objective:*** Although a majority of women (80%) at menopause experience hot flashes, the symptoms' physiological trigger has yet to be identified. To determine the relationship between glucose availability and hot flashes in menopausal women, hot flash frequency was compared between intervals while the subjects were fasting and/or infusing in a sample of menopausal women (38–55 years of age).
- ***Design:*** An experimental study was conducted in 10 postmenopausal women taking hormone therapy (HT) between the ages of 38 and 55. Following a clinic visit to screen for general health and absence of diabetes, HT participants were asked to stop the medication for 7 to 10 days and to maintain a diary of hot flash frequency. When hot flashes were experienced at least four times per day in a consecutive 3-day period, participants were admitted to the General Clinical Research Center for a 30-hour experimental protocol, including frequent blood sampling and two experimental periods of intravenous infusion of glucose or normal saline. Blood glucose levels were manipulated to provide conditions of postprandial versus fasting states.
- ***Results:*** There was a significant reduction in the incidence of hot flashes during the experimental elevation of glucose concentrations (130 to 140 mg/dl) compared to the fasting state (<110 mg/dl) ($t = -2.4$, $df = 9$, $p = .04$).
- ***Conclusions:*** Conditions of fasting may stimulate the trigger mechanism for menopausal hot flashes.

- ***Key Words:*** glucose transport · hot flashes · menopause

The hot flash is the most frequently reported symptom of menopause. It is generally associated with declining estrogen levels related to depletion of ovarian follicles in the aging ovary, although a direct cause and effect relationship between estrogen level and hot flashes has not been demonstrated (Sterns & Hayes, 2002). Furthermore, in most studies absolute concentrations of estrogen neither predict nor correlate with hot flash severity (Freedman, 2002; Hutton, Jacobs, Murray, & James, 1978). While various hypotheses have been proposed, the mechanism is unknown by which estrogen decline at menopause causes activation of sympathetic heat dissipation.

A majority of women (75–80%) undergoing the natural course of menopause and an even greater number of oophorectomized women (95–100%) experience hot flashes associated with the decline in ovarian steroids (Bachmann, 1999). Currently in the United States, there are 20,047,000 women of menopausal age (45–54), of which an estimated 15,035,250 experience hot flashes (United States Census Bureau, 1999). Approximately 3 million of those women seek medical assistance for symptom relief. The current optimal treatment for hot flashes is use of hormone replacement therapy (HT). However, recent findings regarding potential risks in use of HT reported in the Heart and Estrogen Replacement Study II (Grady et al., 2002) and the Women's Health Initiative (Writing group for the Women's Health Initiative Investigators, 2002) create complex decision-making dilemmas for women suffering from hot flashes. Research focused on uncovering the hot flash mechanism has the potential to redirect treatment strategies.

An emerging model based on rat studies suggests that menopausal hot flashes result from transient inadequacies in central nervous system glucose transport (Shi & Simpkins, 1997). The decline in glucose delivery to the brain is a secondary result of diminished estrogen-stimulation of glucose transporter production. With fewer glucose transporter molecules available to maintain adequate glucose transport, the brain receives less glucose. This is further compounded under physiological conditions such as fasting, in which less glucose is

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available for transport. The end result is a transient alteration in available glucose to brain neurons (Shi & Simpkins, 1997). In this paradigm, the hot flash is viewed as a counter-regulatory attempt to increase blood flow and subsequent delivery of glucose to the brain.

The purpose of this study was to examine the research question: *Is there a significant difference in the incidence of menopausal hot flashes between conditions of fasting and experimentally sustained (130 to 140 mg/dl) blood glucose concentrations?*

Theoretical Model

The brain glucose counter-regulatory model (Figure 1) of hot flashes is derived from the central effects of the neuroendocrine changes associated with menopause. These effects are more pronounced during the perimenopause transition, a time of transient and irregular fluctuations of estrogen as the ovary gradually loses its ability to produce a responsive follicle. This irregular estrogen withdrawal gives rise to the symptoms of menopause (Reame, 2000).

At the blood brain barrier, changing estrogen concentrations decrease transcription of glucose transporter 1 (GLUT 1) messenger RNA (Shi & Simpkins, 1997). The GLUT 1 mediates brain glucose uptake from the blood supply (Degroot & Jameson, 2001). With fewer GLUT 1 molecules produced, fewer are available to transport glucose across the blood brain barrier. Using a rodent model, Shi and Simpkins (1997) demonstrated that estrogen-deficient states lead to decreased production of GLUT 1 and subsequent diminished glucose availability in neuroendothelial cells in ovarectomized rats. Furthermore, in rodent models, hot flashes (as measured by changes transient changes in tail color and temperature) can be induced by using a variety of stimuli that reduce blood glucose or block the ability of brain cells to use glucose (Bishop & Simpkins, 1992; Bishop & Simpkins, 1995; Simpkins, Andreadis, Millard, & Katovich, 1990; Simpkins, Katovich, & Millard, 1990). Conversely, elevations in blood glucose prevent the ability to induce the hot flash in the rat model (Simpkins, Katovich, & Millard, 1990).

During periods of fluctuation in glucose delivery, ventromedial glucose-sensing cells in the hypothalamus are triggered to release norepinephrine (Borg et al., 1994). A similar release of norepinephrine is well documented in the physiology of menopausal hot flashes (Freedman & Woodward, 1992); however, the mechanism of the release has not been identified. In the model guiding the present study, the hot flash mechanism cascade stimulates an increase in glucose available to neurons.

The hot flash is the most frequently reported symptom of menopause.

Background

Several models have sought to explain the mechanism by which estrogen withdrawal at menopause causes the inappropriate activation of sympathetic heat dissipation. Early investigators (Casper, Yen, & Wilkes, 1979; Tataryn, Meldrum, Lu, & Judd, 1979) observed hot flashes to be temporally associated with luteinizing hormone (LH) pulses. However, later studies showed that hot flashes occur in women with various conditions where LH is suppressed, including hypophysectomy (Mulley, Mitchell, & Tattersall, 1977) and pituitary insufficiency (Meldrum, Erlik, Lu, & Judd, 1981). Also, hot flashes can occur when LH release is stimulated by gonadotrophin releasing hormone (Casper & Yen, 1981; DeFazio et al., 1983). These observations suggest that hot flashes and LH pulses are coevents in response to other factors.

Investigators, using evidence from animal and human models, have also proposed that hot flashes are caused by a narrow thermoneutral zone causing a central autonomic response (Freedman, 2000). This central response leads to an increase in heart rate, and then the release of cortisol, mineral corticoids, beta-endorphin, and luteinizing hormone (Kronenberg, 1990). Considerable evidence also exists that norepinephrine plays a causal role in the hot flash mechanism. Brück and Zeisberger (1990), who observed that injection of norepinephrine near the rat hypothalamus caused peripheral vasodilation, heat loss, and a decrease in core temperature similar to the events of a hot flash. However, the question remains why norepinephrine is released. The model for the clinical experiment reported here suggests a potential mechanism for norepinephrine release in the hot flash event.

An early study based on this model included observation of three menopausal women for 5 hours after ingestion of a standardized breakfast. Simpkins and Katovich (1989) demonstrated that hot flashes were absent when blood glucose was elevated, but appeared when glucose concentrations fell. Using a larger sample, more precise hot flash measurement, and controlled experimental conditions, the current study provided more robust evidence in support of a brain-glucose interaction in the etiology of hot flashes.

Methods

Participants

Approval of the clinical protocol for use with human subjects was obtained and all volunteers provided written informed consent. This study was conducted in a General Clinical Research Center (GCRC) of a large Midwestern university. Sixteen healthy postmenopausal volunteers were recruited via flyers posted on the university hospital bulletin boards and from a university Web site. With the sample size of 12 participants in each experimental condition, this study provided power (75%) to yield a statistically significant result. Based on a study by Simpkins and Katovich (1989), this computation assumed a

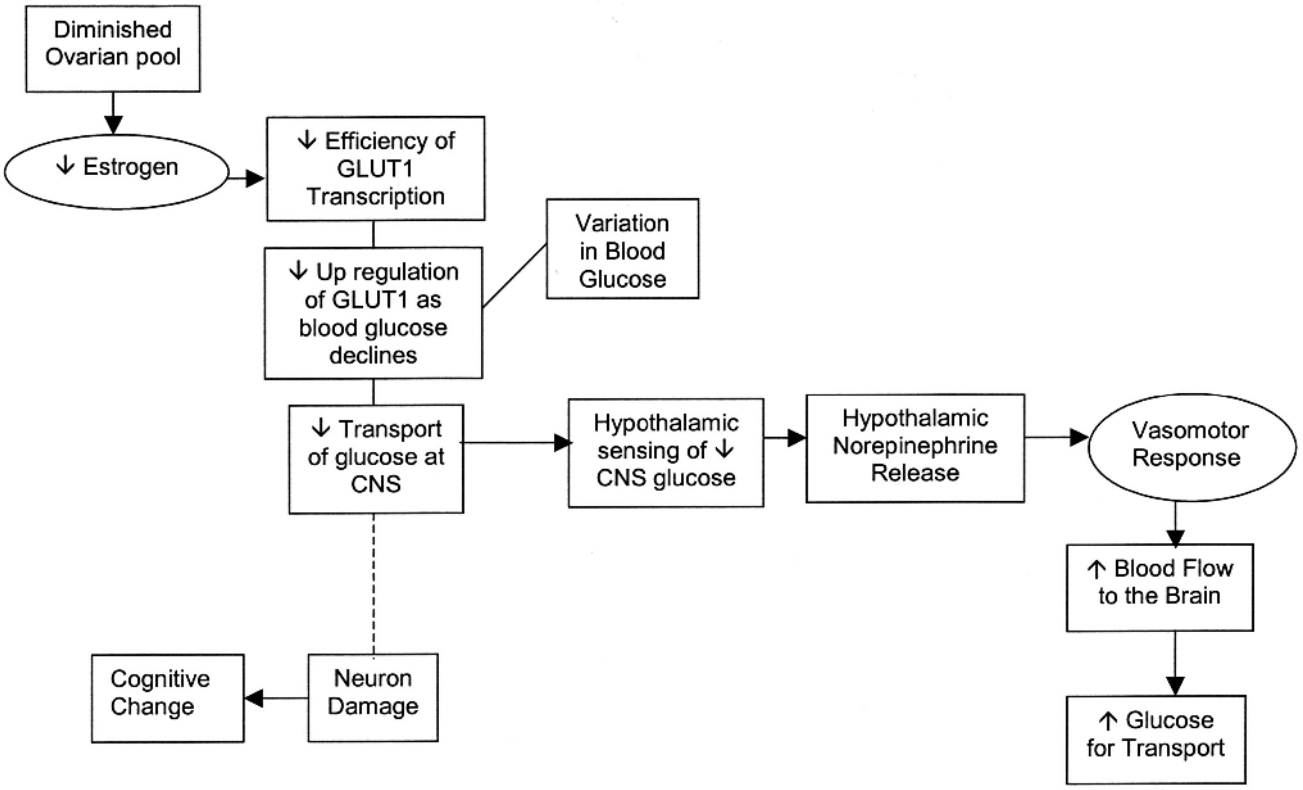

FIGURE 1. The Impaired Glucose Delivery Model of Menopausal Hot Flashes.

mean difference of 2.5 hot flashes between the experimental conditions (*SD*, 3). Twelve women who met the criteria (postmenopausal as defined by the absence of a menstrual period for 12 months, no current medical or psychiatric illness, and no current medication usage) were admitted to the study. To control for factors known to alter the incidence of hot flashes, women who smoked and those with body mass index >31 kg/m^2 or <20 kg/m^2 were excluded. Potential participants were also screened for diabetes. The general health of all potential participants was screened via thorough history and physical exam.

Procedure

Participants were admitted to a GCRC for a 30-hour intensive blood sampling protocol that included 3.5 hour experimental phases on two sequential mornings and one non-fasting observational phase between them. Using an experimental crossover design, each participant was exposed to randomly ordered, experimental periods of glucose and normal saline infusion.

Skin conductance monitoring was initiated at admission using standard application procedures (Carpenter, Andrykowski, Freedman, & Munn, 1999; Dormire & Carpenter, 2001). To collect blood, a heparinized catheter was placed in one forearm with a second catheter placed in the antecubital space of the other arm for infusion of fluids during the experimental periods. The intravenous infusion assigned for that day was initiated using a standard pump set at the initial rate (100 ml/hour). The participant was blinded to the infusion type.

Using the glucose clamp procedure of the methodology of the hyperglycemic glucose clamp (DeFronzo, Tobin, & Andres, 1979; Elahi, 1996; Fanelli, et al., 1998), a variable rate infusion of 20% dextrose maintained the blood glucose level above 130 mg/dl. Samples for blood glucose were drawn every 5 minutes during a 30-minute titration period. The infusion rate of normal saline was randomly adjusted at least four times during the titration period to maintain a sham. Following the titration period, blood glucose was sampled every 15 minutes for the 3-hour monitoring period. Intravenous flow was adjusted to maintain blood glucose above 130 mg/dl during the dextrose infusion (20%), and random rate changes of three per hour were maintained during the normal saline infusion.

Participants rested during the observation period (between the experimental periods) and were fed the same diet because caloric intake was monitored. The caffeine-free diet provided an average caloric intake (1791 ± 158.0 kcal). No foods were served at temperature extremes to avoid stimulating or inadvertently treating hot flashes.

Measurement of Variables

Skin Conductance Decreasing skin resistance is an established objective measure of the menopausal hot flash (Freedman, 2000). In this study hot flash incidence was objectively measured through continuous monitoring using the Biolog® Skin Conductance Monitor (UFI Model 3991/1 SCL, UFI, Morro Bay, CA). A standard criterion of increase in skin conductance (>2 μmhos in <30 seconds) is considered a valid hot flash (Freedman, 1989). Participants also noted per-

ceived hot flashes by pressing a button on the monitor to event mark on the tracing.

Blood Glucose Level For each blood glucose sample, blood (0.5 cc) was drawn from a catheter placed in the dominant forearm and flushed with heparinized saline. A Beckman Glucose Analyzer determined the blood glucose level. The sample of venous blood (0.5 cc) was centrifuged for 20 seconds and unhemolyzed plasma (5 drops) was pipetted into the analyzer (Beckman, 1977).

Reproductive Hormone Assays To confirm menopause status, blood samples for follicle stimulating hormone (FSH) and estradiol (E_2) were collected at admission. An FSH value (>30 mIU/ml) and estradiol level (<20 pg/ml) were used as clinical indicators of postmenopausal status (Reame, 2000).

Data Analysis

The Biolog software program analyzed skin conductance data, using the standard hot flash identification criteria for skin conductance recording (>2 μmhos increase in skin conductance in <30 seconds). In addition, data were collected regarding subjectively identified hot flashes that were not validated by the analysis program (>30 seconds for change to occur or <2 μmhos change). A paired *t* comparison tested the hypothesis that hot flash frequency would be higher with lower blood glucose than when blood glucose was experimentally elevated.

Results

This study examined the research question: *Is there a significant difference in the incidence of menopausal hot flashes between conditions of fasting and experimentally sustained (130 to 140 mg/dl) blood glucose concentrations?* Of the 16 women originally recruited for the study, four were excluded from the protocol (three did not experience hot flashes after discontinuing HT, one had scheduling difficulties). In addition, data from two participants were dropped from the final data analysis because estradiol concentrations did not confirm postmenopausal status and no hot flashes were experienced during any aspect of the study.

Clinical Characteristics The average participant in this study was:

- 48.6 years old
- well educated with 15.4 years of schooling
- 5 years past menopause
- exhibited a body mass index of 25.4

Concentrations of FSH and estradiol were in the expected ranges for postmenopausal women and all laboratory indices of general health were within normal limits. An overview of the clinical characteristics of the final sample of 10 participants is presented in Table 1.

Hot Flash Frequency To be included in the data analysis, participants had to experience at least one hot flash during one of the experimental arms of the protocol, identified either by predetermined changes in skin conductance or by subjective report (Table 2). As expected, mean blood glucose levels during glucose administration were significantly higher compared to those during normal saline infusion (134.35 ± 2.56 mg/dl vs. 85.96 ± 6.62 mg/dl; $t = 23.44$, $df = 9$, $p < .001$). By skin conductance recordings, two participants experienced objectively identified hot flashes during the glucose infusion period (three hot flashes total) while five experienced a total of 23 flashes during normal saline infusion. Hot flash frequency between the two testing periods differed significantly ($t = -2.4$, $df = 9$, $p = .04$). The magnitude of the effect was moderate ($d = -0.699$).

Discussion

This study tested the hypothesis that hot flash frequency varies with blood glucose concentrations. In a sample of 10 postmenopausal women, the incidence of objectively identified hot flashes was significantly reduced when blood glucose concentrations were elevated experimentally. Hot flashes were much more likely to occur during the fasting state. These findings are consistent with those of a small observational study by Simpkins and Katovich (1989) who monitored blood glucose and hot flash incidence after a standardized breakfast in three menopausal participants.

Although the estradiol and FSH levels were in the menopausal range, it is possible that hot flashes of greater intensity would have been experienced if the washout period after dis-

TABLE 1. Clinical Characteristics of the Sample

	Mean ($n = 10$)	*SD*	Range
Age (years)	48.8	5.6	38–55
Education (years)	15.7	2.5	12–20
BMI	25.6	3.6	20.2–30.7
Years last menses	5	5.2	1–14
Screening FBS	88.1 mg/dl	11.4	68–108
HgbA1c	5.2%	0.25	4.7–5.5
30 minute GTT	133.8 mg/dl	21.9	103–173
120 minute GTT	103.7 mg/dl	21.7	83–137
Hematocrit	38.9%	2.09	35.9–41.4
WBC	5.3 K/MM3	1.5	3.0–7.3
Estradiol	15.2 pg/ml	5.1	7–23
FSH	67.9 mIU/ml	41.6	27.5–175.0
Admission FBS	88.0 mg/dl	8.9	76–102

Note. BMI = body mass index; FBS = fasting blood sugar; HgbA1c = hemoglobin A1c; GTT = glucose tolerance test; WBC = white blood count; FSH = follicle stimulating hormone.

TABLE 2. Objective and Subjective Hot Flash Frequency by Participant

	Glucose Infusion ($n = 10$)			Normal Saline Infusion ($n = 10$)		
Participant	*Mean Glucose Conc.*	*Objective Hot Flashes*	*Subjective Hot Flashes*	*Mean Glucose Conc.*	*Objective Hot Flashes*	*Subjective Hot Flashes*
1	134.48	0	0	91.05	6	4
2	132.29	0	1	75.88	0	1
3	130.33	0	0	93.12	0	1
7	132.73	2	0	79.63	5	3
8	137.06	0	0	93.26	7	3
9	133.26	0	3	80.79	0	2
10	134.25	0	0	80.74	0	1
11	138.77	0	3	90.72	0	1
12	133.35	1	1	91.83	2	4
15	137.00	0	0	82.60	3	1
Total Frequency		**3**	**8**		**23**	**21**
Mean	**134.35**	**.30**	**0.80**	**85.96**	**2.30**	**2.10**
SD	**2.56**	**0.68**	**1.23**	**6.62**	**2.79**	**1.28**

Note. Conc. = concentration.

continuation of hormone therapy had been longer prior to enrollment in the protocol. The morning schedule of the experiment may have reduced detection of spontaneous hot flashes. In one observational study, a circadian rhythm in hot flash episodes was demonstrated with the highest frequency at approximately 6:30 p.m. (Freedman, Norton, Woodward, & Cornelissen, 1995).

These findings provide indirect evidence in support of the view that alterations in glucose transport across the blood brain barrier may be a trigger mechanism for menopausal hot flashes. Significantly more hot flashes were experienced when blood glucose was maintained at fasting levels, while few hot flashes occurred when blood glucose was experimentally elevated.

Finally, these findings provide preliminary evidence in development of alternative treatment strategies for hot flashes. Confusion and anxiety about hormone replacement therapy have dominated treatment concerns for women following publication of the findings regarding increased risk for cardiovascular events and invasive breast cancer in both the Heart and Estrogen Replacement Study II (Grady et al., 2002) and the Women's Health Initiative (Writing group for the Women's Health Initiative Investigators, 2002). Our clinical evidence indicates hot flash frequency is suppressed when blood glucose level is within the elevated normal range. As an HT alternative, these findings provide important preliminary information directing the development of a dietary modification treatment strategy aimed at treating the proximate cause of vasomotor instability. ◼

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