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Physiology of Hot Flashes

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ABSTRACT Hot flashes are the most common symptom of the climacteric, although prevalence estimates are lower in some rural and non-Western areas. The symptoms are characteristic of a heat-dissipation response and consist of sweating on the face, neck, and chest, as well as peripheral vasodilation. Although hot flashes clearly accompany the estrogen withdrawal at menopause, estrogen alone is not responsible since levels do not differ between symptomatic and asymptomatic women. Until recently it was thought that hot flashes were triggered by a sudden, downward resetting of the hypothalamic setpoint, since there was no evidence of increased core body temperature. Evidence obtained using a rapidly responding ingested telemetry pill indicates that the thermoneutral zone, within which sweating, peripheral vasodilation, and shivering do not occur, is virtually nonexistent in symptomatic women but normal (about 0.4°C) in asymptomatic women. The results suggest that small temperature elevations preceding hot flashes acting within a reduced thermoneutral zone constitute the triggering mechanism. Central sympathetic activation is also elevated in symptomatic women which, in animal studies, reduces the thermoneutral zone. Clonidine reduces central sympathetic activation, widens the thermoneutral zone, and ameliorates hot flashes. Estrogen virtually eliminates hot flashes but its mechanism of action is not known. Am. J. Hum. Biol. 13:453–464, 2001.

Hot flashes are the most common symptom of the climacteric and occur in the vast majority of postmenopausal women. The prevalence among naturally menopausal women has been reported to be 68% (Neugarten and Kranes, 1965) to 82% (Feldman et al., 1985) in the United States, 60% in Sweden (Hagstad and Jarison, 1986), and 62% in Australia (Guthrie et al., 1996). The median age of onset is approximately 51 years (Kronenberg, 1990). Among ovariectomized women, the prevalence of hot flashes is approximately 90% (Chakravarti et al., 1977; Feldman et al., 1985). Feldman et al. (1985) found that 64% of women in their studies experienced hot flashes for 1–5 years, and Kronenberg (1990) reported the median length of the symptomatic period to be 4 years.

Kronenberg (1990) conducted an extensive questionnaire study of hot flashes in 506 women. Of those reporting current symptoms, 87% had daily hot flashes and one-third of these reported more than 10 per day. Hot flashes generally lasted 1–5 min, with about 6% lasting more than 6 min. About 40% of the women recognized a premonition that a hot flash was about to begin. The experience of a hot flash was most often described as sensations of heat, sweating, flushing, chills, clamminess, and anxiety. Sweating was reported most often in the face, head, neck, and chest, but rarely in the lower body.

Studies of risk factors for menopausal hot flashes have found few strong effects. There is some evidence that thin women who smoked during the premenopausal period are more likely to report hot flashes (Schwingl et al., 1994) than heavier nonsmokers. No significant association has been found between the report of hot flashes and socioeconomic status, age, race, parity, age at menarche, age at menopause, or number of pregnancies (Kronenberg, 1990; Schwingl et al., 1994).

Cultural factors affect the report of hot flashes. Compared to Western women, women from Indonesia report hot flashes at rates of only 10%–20% (van Keep, 1984; Flint and Samil, 1990), Chinese women at rates of 10%–25% (Tang, 1993), and Mexican Mayan women not at all (Beyene, 1986).

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Reasons for these findings are not known. Perhaps women from rural and non-Western cultures demonstrate physiologically defined hot flashes as frequently as Western women but are acculturated in some way to not report them. Or, they may actually have fewer physiologically defined flashes. This could be due to factors such as diet, since some foods such as yams and soy products contain substantial amount of phytoestrogens which may help ameliorate hot flashes (Murkies et al., 1998). The answers to these questions are unknown and represent important avenues for further research.

MEASUREMENT OF HOT FLASHES

A. Skin temperature and blood flow

Peripheral vasodilation, as evidenced by increased skin temperature, occurs during hot flashes in all areas that have been measured. These areas include the fingers, toes, cheek, forehead, forearm, upper arm, chest, abdomen, back, calf, and thigh (Molnar, 1975; Tataryn et al., 1980; Kronenberg et al., 1984; Freedman, 1998). Finger blood flow (Kronenberg et al., 1984) and hand, calf and forearm blood flow (Ginsberg et al., 1981) also increase during hot flashes. Thermographic measurements during hot flashes yielded data similar to those obtained with skin temperature (Studee and Reece, 1979).

B. Sweating and skin conductance

Sweating and skin conductance, an electrical measure of sweating, also increase during hot flashes (Fig. 1). In our laboratory, we measured sweat rate and skin conductance simultaneously from the sternum (Freedman, 1998). Sweat rate was recorded by capacitance hygrometry using a 3.5-cm diameter plastic chamber attached over the sternum. Compressed air, regulated at 200 ml/min, was dried over $CaCO_2$ and passed through the chamber. Skin conductance level was also recorded from the sternum using a 0.5-volt constant voltage circuit and disposable Ag/AgCl electrodes. Both measures increased significantly during 29 hot flashes recorded in 14 women (Fig. 1). Measurable sweating occurred during 90% of the flashes and there was a close time correspondence between both measures. All subjects in the author's studies reside in the Detroit Metropolitan area and are either Caucasian or African-American.

C. Core body temperature

Homeotherms regulate core body temperature between upper thresholds, where sweating and peripheral vasodilation occur, and a lower threshold, where shivering occurs. If core body temperature were elevated in women with hot flashes, their symptoms of sweating and peripheral vasodilation could be explained. However, measurements of esophageal (Kronenberg, 1984), rectal (Molnar, 1975), and tympanic (Tataryn et al., 1980) temperatures were not elevated prior to hot flashes. These studies all found declines of about 0.3°C following hot flashes, probably due to increased heat loss (peripheral vasodilation) and evaporative cooling (sweating). However, esophageal and rectal temperatures have long thermal lag times and might respond too slowly to appear along with the rapid peripheral events of the hot flash (Molnar and Read, 1974). Additionally, it has been shown that tympanic temperature does not reliably measure core body temperature because it is affected by peripheral vasodilation and sweating (Shiraki et al., 1986).

Several studies were conducted in which core body temperature were measured using an ingested radiotelemetry pill, which has a faster response time than the esophageal and rectal methods. The pill is swallowed 90 min before an experiment to allow its egress from the stomach, and the signals are detected by a wire antenna and stored in a small digital recorder. The typical transit time through the gut is about 24 hr, during which the recorder samples the data every 30 sec. Hot flashes are recorded on a separate device, using sternal skin conductance level as the marker.

In the first study, 10 symptomatic women were recorded using ambulatory monitoring for 24 hr (Freedman et al., 1995). Of 77 hot flashes, 46 (60%) were preceded by small, but significant increases in core body temperature. In a second study, conducted during sleep in a temperature-controlled laboratory, 37 hot flashes occurred in 8 postmenopausal women (Freedman and Woodward, 1996). Significant core temperature elevations preceded 24 of the flashes (65%), whereas rectal temperature had not significantly changed (Fig. 2). The results were replicated during a daytime study in the laboratory (Freedman, 1998).

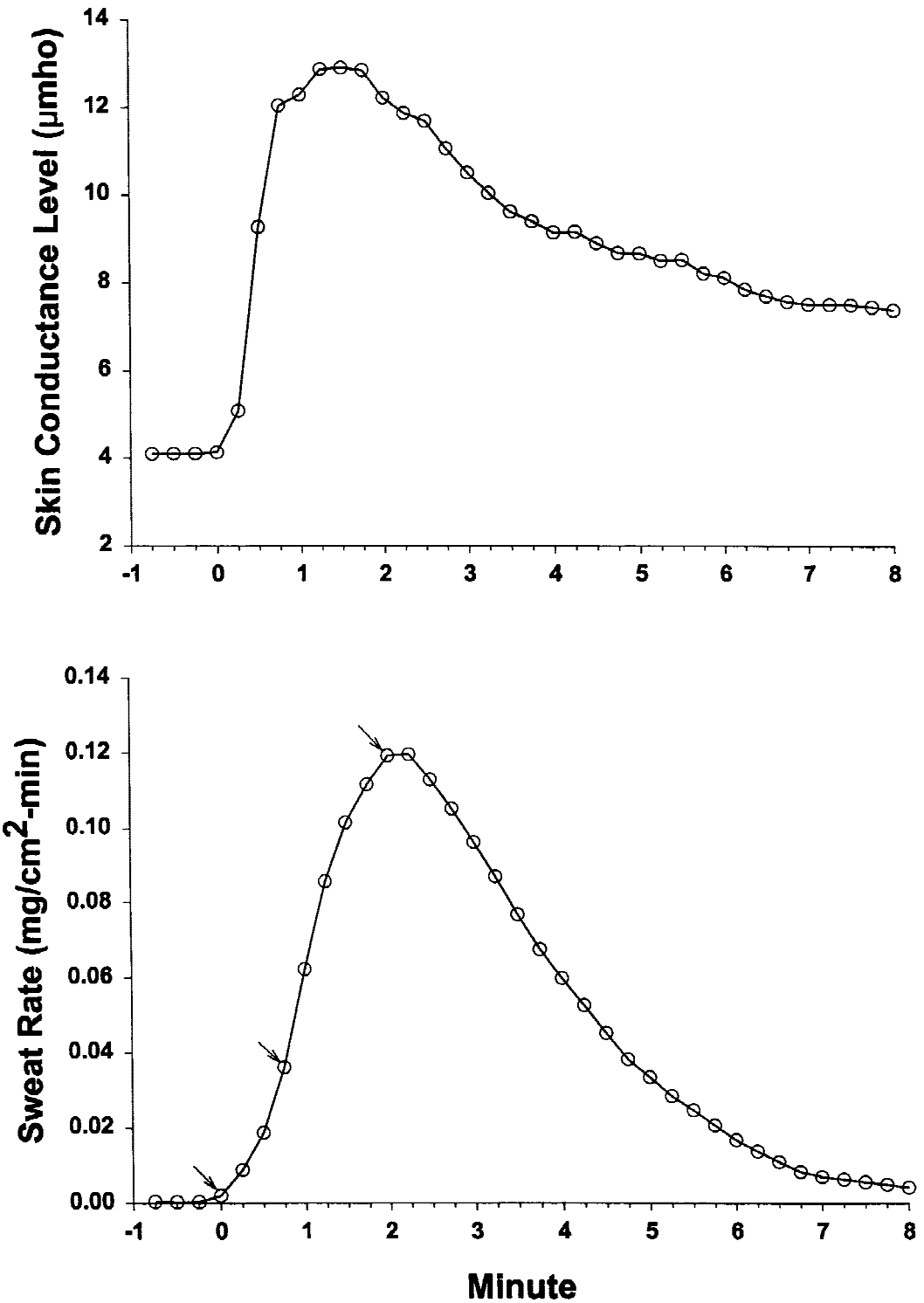

Fig. 1. Time course of skin conductance and sweating in 29 hot flashes in 14 women. From Freedman (1998).

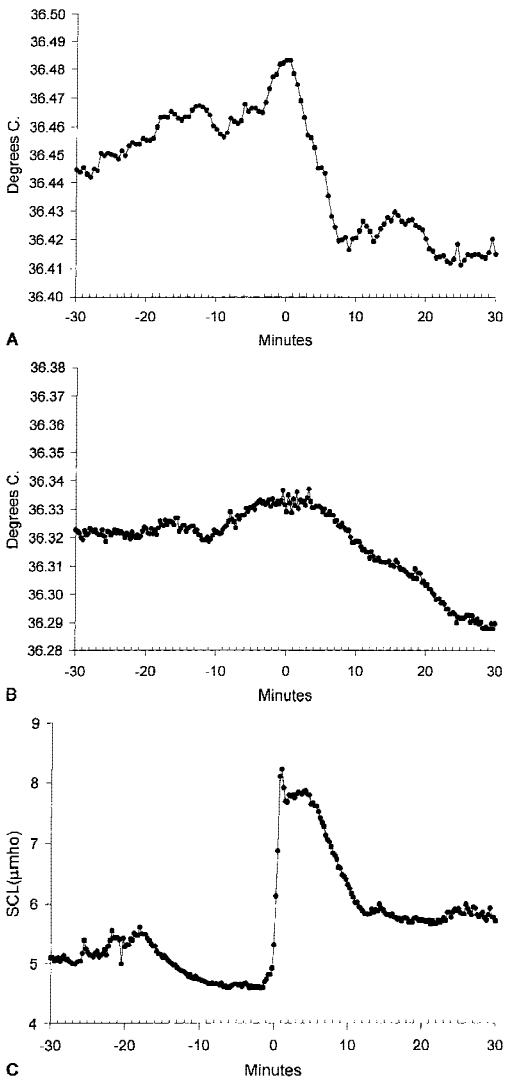

Fig. 2. (A)-Core body temperature (means) recorded from ingested telemetry pills during menopausal hot flashes in 8 women. Time zero is the beginning of the sternal skin conductance response in (C) below. (B)-Rectal temperature (means) during menopausal hot flashes. (C)-Sternal skin conductance (means) during menopausal hot flashes. From Freedman and Woodward (1996).

D. Metabolic rate

Elevations in core body temperature can be caused by increased metabolic rate (heat production) and by peripheral vasoconstriction (decreased heat loss). We sought to determine if either of these factors accounted for the core body temperature elevations preceding hot flashes (Freedman, 1998). Twenty-nine flashes were recorded in 14 postmenopausal women. Significant elevations in metabolic rate (about 15%) occurred but were simultaneous with sweating and peripheral vasodilation and did not precede the core temperature elevations (Fig. 3). Peripheral vasoconstriction did not occur. Thus, increased metabolic rate and peripheral vasoconstriction do not account for the core body temperature elevations.

E. Heart rate

Modest increases in heart rate, about 7–15 beats/minute (Molnar, 1975; Sturdee et al., 1978; Freedman, 1989), occur at approximately the same time as the peripheral vasodilation and sweating.

DEFINING HOT FLASHES PHYSIOLOGICALLY

A. Finger temperature

Temperature from the dorsum of one finger was proposed as the first physiological marker for menopausal hot flashes (Meldrum et al., 1979). In 7 symptomatic women, 41 skin temperature elevations >1°C occurred within approximately 1 min of the subjective hot flash. However, the duration of the temperature elevations averaged 31 min, whereas the duration of subjective flushing was 2.3 min. Also, precise definitions of the onset and offset of the temperature elevations were not reported.

B. Skin conductance

Subsequently, skin conductance recorded from the sternum was investigated as a hot flash marker. Tataryn et al. (1981) found that 98% of 128 subjective flashes in 8 postmenopausal women were accompanied by elevations in sternal skin conductance compared to 82% for finger temperature and 81% for decreased tympanic temperature. All of these changes were significantly reduced by estrogen administration in 4 of the women. However, the precise characteristics of the skin conductance responses were not defined.

Our laboratory subsequently sought to determine these characteristics (Freedman, 1989). Sternal skin conductance level, finger temperature, and heart rate were recorded for 4 hr in 11 postmenopausal and 8 premenopausal women. Twenty-nine subjective hot flashes were indicated by push-button in the first group. All of these were

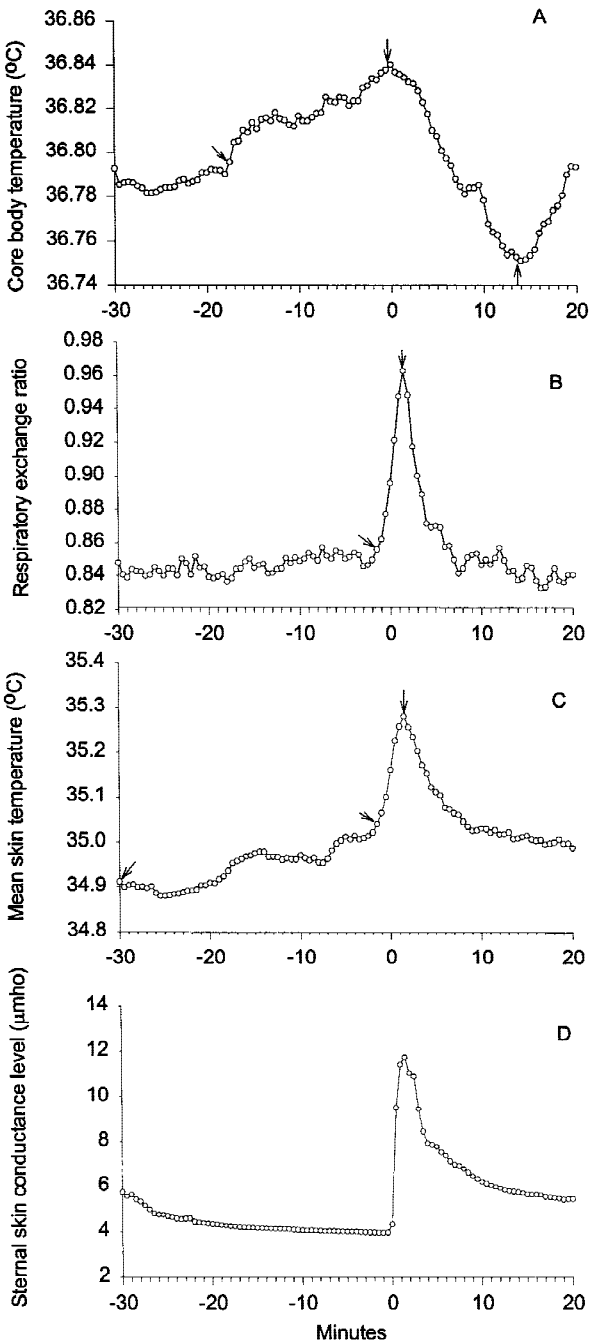

Fig. 3. (A)-Core body temperature (means) during menopausal hot flashes in 14 women. Time 0 is the beginning of the sternal skin conductance response in (D), below. Intervals between arrows are significantly different from each other at $p < .05$, Duncan's test. From Freedman (1998). (B)-Respiratory exchange ratio (means) during hot flashes. (C)-Mean skin temperature (means) during hot flashes. (D)-Sternal skin conductance (means) during hot flashes.

accompanied by an increase in sternal skin conductance ≥ 2 μmho/30 sec. One skin conductance elevation occurred without a button press. All skin conductance elevations occurred within 66 sec of the button press. No skin conductance elevations occurred in the premenopausal women. Thus, there was a concordance of 95% between the skin conductance criterion and the subjects' reports. Significant elevations in skin temperature

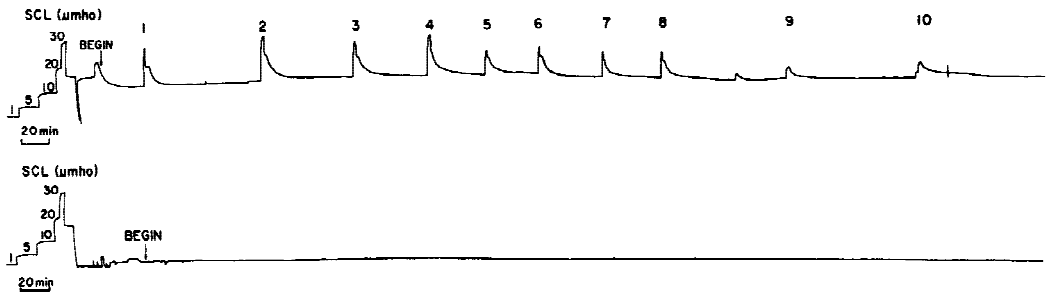

Fig. 4. Ambulatory skin conductance recordings showing 10 hot flashes in a symptomatic woman (top) and none in an asymptomatic woman (bottom). From Freedman (1989).

and heart rate occurred during the flashes but were not as sensitive or specific as the skin conductance elevations.

We replicated these findings in 18 symptomatic and 8 asymptomatic postmenopausal women (Freedman et al., 1992). There was a concordance of 80% between the sternal skin conductance criterion (2 μmho/30 sec) and the subjective reports (button press) in 15 flashes recorded in the symptomatic women. No events occurred in the asymptomatic women.

These findings were then independently replicated by another laboratory (deBakker and Everaerd, 1996). In two separate studies of 20 symptomatic women, a concordance of 90% was obtained between the sternal skin conductance criterion and subjective reports. Measurements of finger temperature and blood flow were less predictive and did not improve the concordance rate when added to the skin conductance measure.

C. Ambulatory monitoring

To evaluate treatment studies it would be useful to have a method that could be used outside the laboratory over longer periods of time. We therefore developed methods for recording sternal skin conductance on ambulatory monitors for 24 hr. Using the same basic circuit and electrodes we found a concordance of 86% between the skin conductance criterion and button presses in 43 flashes recorded in 7 symptomatic women (Freedman, 1989). No such changes occurred in the 8 premenopausal women (Fig. 4).

These findings were replicated in a second study (Freedman et al., 1992). A concordance of 77% was obtained in 149 flashes recorded in 10 symptomatic women. Twelve skin conductance responses occurred in 8 putative asymptomatic women, representing a false response rate of about 8%.

These ambulatory monitoring procedures were then successfully used to demonstrate the efficacy of a behavioral treatment for hot flashes in two subsequent studies (Freedman and Woodward, 1992; Freedman et al., 1995).

D. Provocation techniques

For laboratory investigations, it would be useful to reliably provoke hot flashes as opposed to waiting for them to occur during extended recording periods. Sturdee (1978) observed that peripheral warming provoked objective and subjective hot flashes in 7 of 8 symptomatic women. We, therefore, sought to operationally define this procedure. Two 40 × 60 cm circulating water pads maintained at 42°C were placed on the torso of 11 supine symptomatic women in a 23°C room (Freedman, 1989). Eight hot flashes occurred within 30 min. A concordance of 73% was obtained between the skin conductance criterion (2 μmho/30 sec) and subjective report (button press). These findings were replicated in a subsequent study in 14 symptomatic women with a concordance of 84%. In this study, 25 hot flashes occurred during a 45-min heating period. No objective or subjective responses occurred in 8 asymptomatic women.

ENDOCRINOLOGY

A. Estrogens

Since hot flashes accompany the decline of estrogens in the vast majority of naturally and surgically menopausal women, there is little doubt that they play a role in the genesis of hot flashes. However, estro-

gens alone do not appear responsible for hot flashes since there is no correlation between the presence of this symptom and plasma (Askel et al., 1976), urinary (Stone et al., 1975), or vaginal (Stone et al., 1975) levels. No differences in unconjugated plasma estrogen levels were found in symptomatic versus asymptomatic women (Hutton et al., 1978). Additionally, clonidine significantly reduces hot flash frequency without altering circulating estrogen levels (Schindler et al., 1979). Nevertheless, estrogen administration in hormone replacement therapy virtually eliminates hot flashes (Kennemans et al., 1996; Johnson, 1998).

B. Gonadotropins

Since gonadotropins become elevated at menopause, their possible role in the initiation of hot flashes was investigated. Although no differences in LH levels were found between women with and without hot flashes (Campbell, 1976), a temporal association was found between LH pulses and hot flash occurrence (Casper et al., 1979; Tataryn et al., 1979). However, subsequent investigation revealed that women with a defect of GnRH secretion (isolated gonadotropin deficiency) had hot flashes but no LH pulses and women with abnormal input to GnRH neurons (hypothalamic amenorrhea) had some LH pulses but no hot flashes (Gambone et al., 1984). Additionally, hot flashes occur in hypophysectomized women, who have no LH release (Mulley et al., 1977), in women with pituitary insufficiency and hypoestrogenism (Meldrum et al., 1981), and in women with LH release suppressed by GnRH analog treatment (Casper and Yen, 1981; DeFazio et al., 1983).

C. Opiates

It was observed that alcohol-induced flushing in subjects taking chlorpropamide, a drug that stimulates insulin release and lowers blood glucose, was related to opiate receptor activation (Leslie et al., 1979). Lightman et al. (1981) subsequently found that naloxone infusion significantly reduced hot flash and LH pulse frequencies in 6 postmenopausal women. However, DeFazio et al. (1984) attempted to replicate this study and found no effects. Thus, there is no consistent evidence of the involvement of an opioidergic system in menopausal hot flashes.

D. Catecholamines

There is considerable evidence that norepinephrine plays an important role in thermoregulation mediated, in part, through α_2-adrenergic receptors (Brück and Zeisberger, 1990). Injection of norepinephrine into the preoptic hypothalamus causes peripheral vasodilation, heat loss, and a subsequent decline in core body temperature (Brück and Zeisberger, 1990). Additionally, there is considerable evidence that gonadal steroids modulate central noradrenergic activity (Insel and Motulskey, 1987). Studies of plasma norepinephrine have not found increased levels prior to or during hot flashes (Casper et al., 1979; Kronenberg et al., 1984). However, brain norepinephrine levels cannot be measured in plasma, due to the large amounts derived from peripheral organs (Lambert et al., 1995). We, therefore, measured plasma MHPG (3-methoxy-4-hydroxyphenylglycol), the main metabolite of brain norepinephrine, to determine if central norepinephrine levels were elevated during hot flashes (Freedman and Woodward, 1992). We studied 13 symptomatic and 6 asymptomatic postmenopausal women who were supine with an IV line in a 23°C room. Basal MHPG levels were significantly higher in the symptomatic women and increased significantly during resting and heat-induced flashes. There were no hot flashes or significant MHPG changes in the asymptomatic women.

However, approximately 50% of the free MHPG that enters the blood is metabolized peripherally to vanillylmandelic acid (VMA), and VMA formation can compete with MHPG production (Kopin et al., 1984). Thus, fluctuations in peripheral VMA formation could potentially distort measurements of plasma MHPG. Therefore, we measured both compounds simultaneously before and after hot flashes in 14 symptomatic women (Freedman, 1998). Plasma MHPG levels increased significantly ($P < 0.02$) between the preflash (3.7 ± 1.4 ng/ml) and postflash (5.1 ± 2.3 ng/ml) blood samples whereas VMA levels did not significantly change (6.2 ± 1.8 ng/ml vs. 6.1 ± 2.5 ng/ml). Thus there is evidence of increased brain norepinephrine levels before hot flashes, and these levels significantly increase when a flash occurs.

Clonidine, an α_2-adrenergic agonist, reduces central noradrenergic activation and

hot flashes (Schmitt, 1977; Laufer et al., 1982; Clayden et al., 1984). Yohimbine, an α_2-adrenergic antagonist, increases central noradrenergic activation. We sought to determine if clonidine would ameliorate hot flashes and if yohimbine would provoke them in controlled laboratory conditions (Freedman et al., 1990). Nine symptomatic postmenopausal women, aged 43–63 years, served as subjects. Six asymptomatic women, aged 46–61 years, served as a comparison group. All women were in good health and had been amenorrheic for ≥2 years.

In two blind laboratory sessions, subjects received either intravenous clonidine HCl (1 μg/kg) or placebo followed by a 60-min waiting period and then by 45 min of peripheral heating. In two additional blind sessions, subjects received yohimbine HCl (0.032–0.128 mg/kg intravenously) or placebo. Clonidine significantly ($P = 0.01$) increased the length of heating time needed to provoke a hot flash compared to placebo (40.6 ± 3.0 min vs. 33.6 ± 3.6 min) and reduced the number of hot flashes that did occur (2 vs. 8). In the symptomatic women, six hot flashes occurred during the yohimbine sessions and none during the corresponding placebo sessions, a statistically significant difference ($P < 0.015$). No hot flashes occurred in the asymptomatic women during either session.

These data support the hypothesis that α_2-adrenergic receptors within the central noradrenergic system are involved in the initiation of hot flashes and are consistent with the idea that brain norepinephrine is elevated in this process. Animal studies have shown that yohimbine increases norepinephrine release by blocking inhibitory presynaptic α_2-adrenergic receptors (Goldberg and Robinson, 1983). These autoreceptors mediate the turnover of norepinephrine through a feedback mechanism, and a reduction in their number and/or sensitivity would result in increased norepinephrine release (Stark et al., 1989).

This mechanism is consistent with human studies showing that yohimbine elevates and clonidine reduces plasma levels of MHPG (Charney et al., 1982). Therefore, the yohimbine provocation, and clonidine inhibition of hot flashes in symptomatic women may reflect a deficit in inhibitory α_2-adrenergic receptors not seen in asymptomatic women. Additionally, the injection of clonidine into the hypothalamus reduces body temperature and activates heat conservation mechanisms, effects that are blocked by yohimbine (Zacny, 1982). Thus, α_2-adrenoceptors in the hypothalamus may be responsible for the events of the hot flash that are characteristic of a heat dissipation response.

There is considerable evidence demonstrating that estrogens modulate adrenergic receptors in many tissues. It is possible, therefore, that hypothalamic α_2-adrenergic receptors are affected by the estrogen withdrawal associated with the menopause. As noted above, a decline in inhibitory presynaptic α_2 receptors would lead to increased central norepinephrine levels, and this is consistent with evidence from animal studies.

THERMOREGULATION AND HOT FLASHES

Increased thermosensitivity at menopause has been noted in the literature for many years and is reflected in reports of increased hot flash frequency and duration during warm weather (Molnar, 1981; Kronenberg and Barnard, 1995). Peripheral heating has been demonstrated to provoke hot flashes in most of our symptomatic subjects (Freedman, 1989), and this has been found by others as well (Sturdee et al., 1978). As noted earlier, core body temperature (T_c) in homeotherms is regulated by hypothalamic centers between the thresholds of T_c for sweating and peripheral vasodilation and shivering. According to this mechanism, the heat dissipation responses of hot flashes (sweating, peripheral vasodilation) would be triggered if body temperature were elevated or the sweating threshold lowered.

We previously demonstrated that peripheral heating induced hot flashes in symptomatic but not asymptomatic postmenopausal women nor in premenopausal women (Freedman, 1989; Freedman et al., 1992). These data suggested that the sweating threshold was reduced in symptomatic postmenopausal women. Considerable research in humans and animals has shown that conditions which alter the sweating threshold, tend to alter the shivering threshold in the same direction (Brück and Zeisberger, 1990). We therefore tested to see if the T_c shivering threshold was reduced in symptomatic women, similar to their reduc-

TABLE 1. Sweating thresholds, shivering thresholds, and inter-threshold zones for rectal temperature, telemetry pill temperature, and mean body temperature (means ± SE)

	Sweating	Shivering	Inter-threshold
	Rectal Temperature (°C)		
Symptomatic (n = 12)	37.4 ± 0.06	37.4 ± 0.06	0.0 ± 0.06
Asymptomatic (n = 8)	37.7 ± 0.05	37.3 ± 0.16	0.4 ± 0.18
P value[a]	0.001	NS	0.005
	Telemetry Pill Temperature (°C)		
Symptomatic (n = 12)	37.2 ± 0.09	37.2 ± 0.15	0.0 ± 0.11
Asymptomatic (n = 8)	37.5 ± 0.14	37.1 ± 0.09	0.4 ± 0.18
P value	0.008	NS	0.005
	Mean Body Temperature (°C)		
Symptomatic (n = 12)	37.2 ± 0.07	36.4 ± 0.06	0.8 ± 0.09
Asymptomatic (n = 8)	37.6 ± 0.04	36.1 ± 0.18	1.5 ± 0.20
P value	0.0003	0.02	0.0006

[a]P values for group differences, unpaired t-tests.

tion in sweating threshold. We found that the shivering threshold was elevated rather than reduced in symptomatic compared to asymptomatic women (Freedman and Woodward, 1995). This implies that the thermoneutral zone is narrowed in postmenopausal women with hot flashes. This hypothesis would explain the ability of small T_c elevations, as we found with the telemetry pill, to trigger the heat loss mechanisms of the hot flash (sweating, cutaneous vasodilation) and would also explain the shivering observed following many of them. We therefore measured the thermoneutral zone in symptomatic and asymptomatic postmenopausal women, hypothesizing a reduction in the former group.

We studied 12 symptomatic and 8 asymptomatic postmenopausal women (Freedman and Krell, 1999). We measured body temperature using a rectal probe, the ingested telemetry pill, and a weighted average of rectal and skin temperatures and determined the sweating and shivering thresholds for each. In a subsequent session, we raised body temperature to the sweating threshold using exercise. The symptomatic women had significantly smaller inter-threshold zones that the asymptomatic women on all three measures of body temperature (Table 1). Sweat rates were significantly higher in the former group. During exercise, all of the symptomatic and none of the asymptomatic women demonstrated hot flashes.

Animal studies have shown that increased brain norepinephrine narrows the width of the inter-threshold zone (Brück and Zeisberger, 1990). Conversely, clonidine reduces norepinephrine release, raises the sweating threshold, and lowers the shivering threshold in human studies (Delaunay et al., 1993). Thus, we suggest that elevated brain norepinephrine narrows the thermoregulatory inter-threshold zone in symptomatic postmenopausal women. This zone was so small as to be virtually zero using our methods. We propose that small elevations in core body temperature trigger hot flashes when the sweating threshold is crossed. Core body temperature falls following hot flashes, and patients often report shivering at this time. This likely represents the point where the shivering threshold is crossed, although this has not been directly measured.

CIRCADIAN RHYTHMS

The circadian rhythm of T_c is well known, and similar variations in other thermoregulatory parameters, such as heat conductance and sweating, have also been shown. These patterns suggest that the thermoregulatory effector responses of hot flashes might also demonstrate temporal variations. A previous study showed circadian rhythmicity of self-reported hot flashes in some menopausal women, but no physiological data were collected (Albright et al., 1989). We recruited and screened ten symptomatic and 6 asymptomatic postmenopausal women (Freedman et al., 1995). Each received 24-hr ambulatory monitoring of sternal skin conductance level to detect hot flashes as well as ambient temperature, skin temperature, and T_c. The last measure was recorded using the ingested radiotelemetry pill. Cosinor analysis demonstrated a circadian rhythm ($P < 0.02$) of hot flashes with a peak around 1825 hours (Fig. 5). This rhythm lagged the circadian rhythm of T_c in symptomatic women by about 3 hr. T_c values of the symptomatic women were lower than those of the asymptomatic women ($P < 0.05$) from 0000 to 0400, and at 1500 and 2200 hours. The majority of hot flashes were preceded by elevations in T_c, a statistically significant effect ($P < 0.05$). Hot flashes began at significantly ($P < 0.02$) higher levels of T_c (36.82 ± 0.04°C) compared to all non-

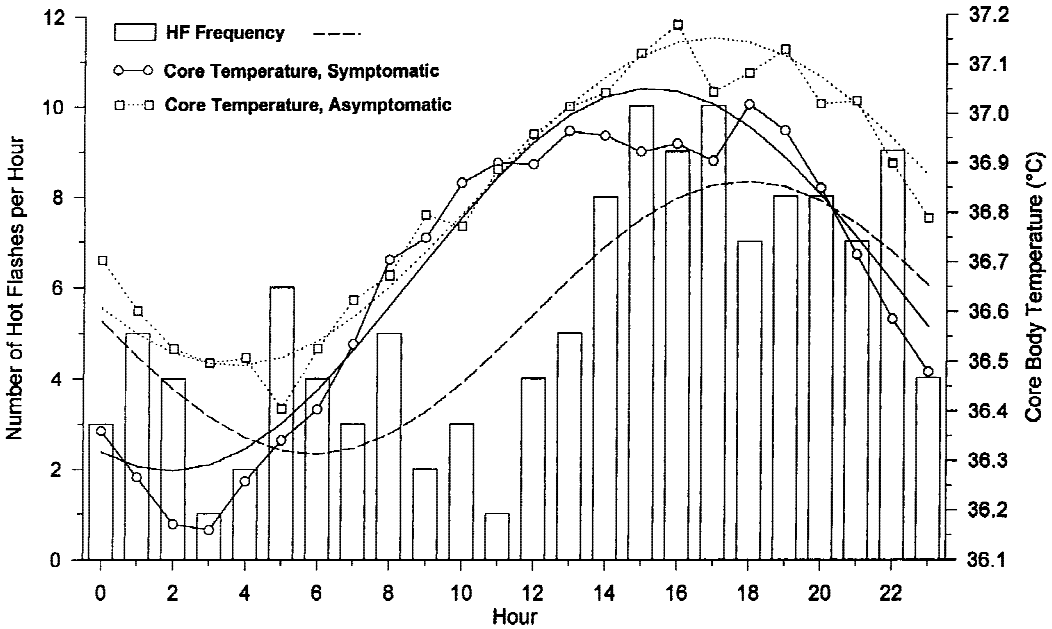

Fig. 5. Hot flash frequency and core body temperature over 24 hours. Hot flash frequency in 10 symptomatic women shown as bars. Best-fit cosine curve for hot flash frequency as a dashed line (----). 24-hour core temperature data for 10 symptomatic women as solid line (o____o) with best-fit cosine curve (_____). 24 hour core temperature data in 6 asymptomatic women as a dotted line (□....□) with best-fit cosine curve (....). From Freedman et al., (1995).

flash periods (36.70 ± 0.005°C). These data are consistent with the hypothesis that elevated T_c serves as part of the hot flash triggering mechanism.

CONCLUSION

Hot flashes are the most common symptom of the climacteric, but their underlying physiological mechanisms are not completely understood. Although hot flashes accompany the estrogen withdrawal at menopause, the levels of estrogens in plasma, urine, and the vagina do not correlate with the presence or absence of hot flashes. Therefore, other factors must be involved.

Since a hot flash is a physiological heat dissipation response an obvious trigger would be a prior elevation of T_c. Earlier researchers did not find such T_c elevations using recordings of rectal, esophageal, and tympanic temperature. However, rectal and esophageal temperature change very slowly and might have missed episodic T_c elevations. Tympanic temperature is affected by facial sweating, an obvious problem in hot flash research. Using an ingested telemetry pill, which responds more rapidly than rectal and esophageal measures, we identified small but significant T_c elevations preceding the majority of hot flashes.

T_c in homeotherms is regulated between upper thresholds for sweating and cutaneous vasodilation and lower thresholds for shivering and vasoconstriction. Between these thresholds is a thermoneutral or "null" zone, within which major thermoregulatory adjustments do not occur. We reasoned that, if this zone were sufficiently narrow in symptomatic women, the T_c elevations could trigger the hot flashes. We then measured the thermoneutral zone and found it to be zero in symptomatic women and 0.4°C in asymptomatic women.

What accounts for this? Animal studies have shown that increased brain norepinephrine (NE) narrows the thermoneutral zone, and we found evidence of elevated brain NE in symptomatic women. Furthermore, clonidine reduces brain NE, raises the sweating threshold, and ameliorates hot flashes.

It has been shown that brain NE increases with age, and this might be responsible for narrowing the thermoneutral zone.

However, it does not explain the absence of hot flashes in asymptomatic women of the same age. Studies of the effects of aging on thermoregulation have been inconsistent, and most do not adequately account for menopause or the menstrual cycle. Hot flashes do not persist until the end of life, but there have been no studies of their offset. These questions present interesting avenues for further research and may help solve the physiological riddle of this very common symptom.

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